

**Specification**

Novel 2-heteroaryl substituted benzimidazole derivative.

**The Field of Technology**

This invention relates to the following, namely, glucokinase activator containing as effective ingredient 2-heteroaryl substituted benzimidazole, which is useful in field of medicine. Furthermore, it relates to a novel 2-heteroaryl substituted benzimidazole derivative.

**Background technique.**

Glucokinase (GK) (ATP : D-hexose 6-phosphotransferase, EC2.7.1.1) is one of the 4 types of kinases of mammals (hexokinase IV). The hexokinase is the enzyme of the first step of the glycolytic pathway and catalyses the reaction from glucose to glucose-6-phosphate. The expression of glucokinase is mainly localised in liver and pancreatic  $\beta$  cells, and plays an important role in the glucose metabolism of the whole body by controlling the rate limiting step of the glucose metabolism of these cells. The glucokinases from liver and pancreatic  $\beta$  cells have different sequences of the N-terminal 15 amino acids due to difference in splicing, however, enzymatic characteristics are the same. In three hexokinases (I, II and III) other than glucokinase, the enzyme activity reaches saturation at glucose concentration of 1 mM or less, whereas the  $K_m$  of glucokinase with respect to glucose is 8 mM which is close to the physiological blood sugar value. Accordingly, in the form of responding to the blood sugar change from normal blood sugar (5 mM) to elevated blood sugar after meals (10-15 mM), facilitation of intracellular glucose metabolism takes place via glucokinase.

A hypothesis has been proposed from about 10 years ago, wherein the glucokinase acts as the glucose sensor of liver and pancreatic  $\beta$  cells [cf. for example, Garfinkel et al., Computer modeling identifies glucokinase as glucose sensor of pancreatic  $\beta$ -cells, American journal Physiology), Vol. 247 (3Pt2), 1984, pp. 527-536].

It is becoming clear from the recent results of glucokinase gene manipulation mice that in fact, the glucokinase plays an important role in the glucose homeostasis of whole body. The mouse in which glucokinase gene has been destroyed dies shortly after birth [cf. for example. Transgenic Knockouts reveal a critical requirement for pancreatic  $\beta$ -cell glucokinase in maintaining glucose homeostasis, Cell, Vol. 83, 1995, pp. 69-78], on the other hand, in the normal and diabetes mellitus mice that overexpressed glucokinase, the blood glucose level becomes low [cf. for example. Ferre T, et al. Correction of diabetic alterations by glucokinase, Proceedings of the National Academy of Sciences of the U.S.A., Vol. 93, 1996, pp. 7225-7230].

As a result of increase in the glucose concentration, although the reactions of the liver and the

pancreatic  $\beta$  cell differ, both responds in the direction of lowering the blood sugar. The pancreatic  $\beta$  cell starts to secrete more insulin, and the liver takes in sugar and stores as glycogen and at the same time, lowers the sugar release.

In this way, the fluctuation of glucokinase enzyme activity plays an important role in glucose homeostasis of mammals through liver and pancreatic  $\beta$  cell. In the cases that develop diabetes mellitus in youth, called MODY2 (maturity-onset diabetes of the young), a mutation in glucokinase gene is discovered, and the lowered activity of glucokinase becomes the cause of blood sugar elevation [cf. for example, Vionnet N. et al., nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus, *Nature Genetics*, Vol. 356, 1992, pp. 721-722].

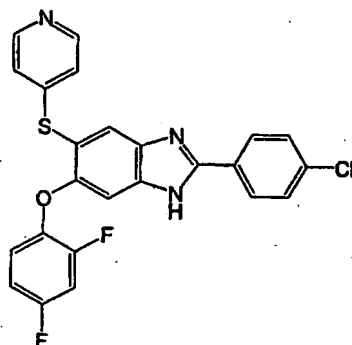
On the other hand, the lineage having mutation that increases glucokinase activity is also found, and such persons display hypoglycemic symptoms (cf. for example, Glaser B, et al, Familial hyperinsulinism caused by an activating glucokinase mutation, *New England Journal Medicine*, Vol. 338, 1998, pp. 226-230].

From these, glucokinase also functions as glucose sensor in human and plays an important role in glucose homeostasis. On the other hand, blood glucose control using glucokinase sensor system is regarded as possible in many type II diabetics. Because the glucokinase activator can be expected to have insulin secretion facilitation action of pancreatic  $\beta$  cell and sugar up take facilitation and sugar release suppression action by the liver, it is considered as useful as therapeutic drug for the type II diabetes mellitus patients.

Recently, it became clear recently that pancreatic  $\beta$  cell type glucokinase was expressed in rat brain, in particular, located in the feeding centre (Ventromedial hypothalamus, VMH). About 20% of VMH is called glucose responsive neurons, and has been considered from the past to play an important role in body weight control. When glucose is administered to rat brain, the food consumption falls, whereas, when the glucose metabolism is suppressed by intracerebral administration of glucosamine, an glucose analogue, overfeeding is observed. From electrophysiological experiments, the glucose responsive neurons are activated in response to physiological glucose concentration change (5-20 mM), however, when the glucose metabolism is suppressed with glucosamine or the like, activity suppression is observed. As the glucose concentration detection system of VHM, a mechanism via glucokinase similar to the insulin secretion of pancreatic  $\beta$  cell is assumed. Accordingly, a substance that activates the glucokinase of VHM in addition to liver and pancreatic  $\beta$  cell has a potential to correct obesity that becomes a problem in may type II diabetic mellitus patients as well as the blood sugar correction effect.

From the above description, the compound having glucokinase activation action is useful as therapeutic agent and/or preventive agent of diabetes mellitus, or as therapeutic agent and/or preventive agent of chronic complication of diabetes mellitus such as retinopathy, nephropathy, neurosis, ischemic cardiac disease, arteriosclerosis or the like, and moreover as therapeutic agent and/or preventive agent of obesity.

As far as benzimidazole derivative is concerned, for example, compounds represented by following formula

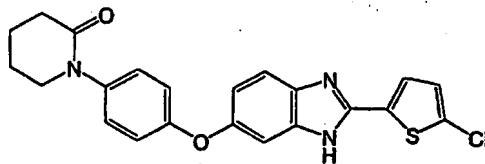


have been described (cf. for example Kokai 2000-026430).

Although the compound described by the aforesaid formula has a substituent at the 2 position of benzimidazole skeleton, the substituent thereof is 4-chlorophenyl and it is different from the A ring in accordance with this invention.

Moreover, the application of the said compound relates to interleukin production suppression, and there is no description that the said compound is useful for the therapy and/or prevention of diabetes mellitus, nor, there is a description suggesting this.

Moreover, as far as benzimidazole derivative is concerned, for example, compounds represented by following formula



are described (cf, for example, W O2004-017963).

The compound described by the aforesaid formula contains only one substituent on benzene ring of the benzimidazole skeleton, moreover although it has a substituent in 2 position of the benzimidazole skeleton, the substituent thereof is 5-chlorothiophenyl, and it is different from the A  
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ring in accordance with this invention.

Moreover, the application of the said compound relates to Factor Xa and Factor VIIa inhibitors, and there is no description that the said compound is useful for the therapy and/or prevention of diabetes mellitus, nor, there is a description suggesting this.

### Disclosure of the invention.

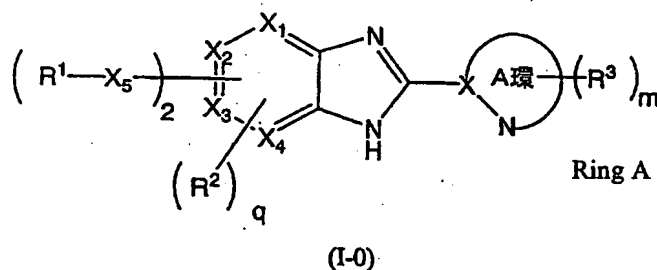
#### **Problems to be overcome by this Invention.**

The object of this invention is to put forward novel 2-heteroaryl substituted imidazole derivative and glucokinase activator using this and in particular to put forward a therapeutic agent and/or preventive agent of diabetes mellitus and obesity.

These inventors carried out assiduous investigation in order to develop a novel diabetes mellitus drug which has drug efficacy exceeding the preexisting diabetes mellitus drug due to different action from aforesaid preexisting drugs, and a novel diabetes mellitus drug having new efficacy, as a result, the novel 2-heteroaryl substituted benzimidazole derivative has glucokinase activation action. This invention was completed based on this discovery.

Namely, this invention relates to the following:

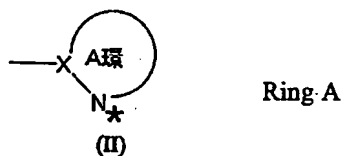
(1) A compound represented by Formula (I-0), or pharmacologically acceptable salts thereof



(wherein, X denotes a carbon atom or nitrogen atom,

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> each independently denote carbon atom or nitrogen atom,

A ring denotes a 5-6 membered nitrogen containing heteroaromatic ring represented by formula (II)



which may containing 1-3 heteroatoms selected from nitrogen atom, sulfur atom and oxygen



atom in the ring (excluding the nitrogen atom represented by N\* in formula II), or a bicyclic ring in which the said nitrogen containing heteroaromatic ring and phenyl or pyridyl are condensed,

R<sup>1</sup> denotes aryl or a 4-10 membered monocyclic or bicyclic heterorings containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said R<sup>1</sup> may be each independently substituted with 1 to 3 R<sup>4</sup>, moreover, when the said heteroring is an aliphatic heteroring, it may contain 1 or 2 double bonds),

R<sup>2</sup> each independently denote hydroxy, formyl, -CH<sub>3-a</sub>F<sub>a</sub>, -OCH<sub>3-a</sub>F<sub>a</sub>, amino, CN, halogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>1-4</sub>OH,

R<sup>3</sup> denotes -C<sub>1-6</sub> alkyl, -(CH<sub>2</sub>)<sub>1-6</sub>-OH, -C(O)-OC<sub>1-6</sub> alkyl, -(CH<sub>2</sub>)<sub>1-6</sub>-OC<sub>1-6</sub> alkyl, -(CH<sub>2</sub>)<sub>1-6</sub>-NH<sub>2</sub>, cyano, -C(O)-C<sub>1-6</sub> alkyl, halogen, -C<sub>2-6</sub>alkenyl, -OC<sub>1-6</sub>alkyl, -COOH, -OH or oxo,

R<sup>4</sup> each independently,

-C<sub>1-6</sub> alkyl (the said alkyl may be substituted with the same or different 1 to 3 hydroxy, halogen,

-OC(O)-C<sub>1-6</sub> alkyl (the said alkyl may be substituted with 1 to 3 halogen), or -OC<sub>1-6</sub> alkyl)

-C<sub>3-7</sub> cycloalkyl,

-C<sub>2-6</sub> alkenyl,

-C(O)-N(R<sup>51</sup>)R<sup>52</sup>,

-S(O)<sub>2</sub>-N(R<sup>51</sup>)R<sup>52</sup>,

-O-C<sub>1-6</sub> alkyl (the said C<sub>1-6</sub> alkyl may be substituted with halogen or N(R<sup>51</sup>)R<sup>52</sup>),

-S(O)<sub>0-2</sub>-C<sub>1-6</sub> alkyl,

-C(O)-C<sub>1-6</sub> alkyl (the said C<sub>1-6</sub> alkyl may be substituted with halogen, amino, CN, hydroxy, -O-C<sub>1-6</sub> alkyl, -CH<sub>3-a</sub>F<sub>a</sub>, -OC(O)-C<sub>1-6</sub> alkyl, -N(C<sub>1-6</sub> alkyl)C(O)O-C<sub>1-6</sub> alkyl, -NH-C(O)O-C<sub>1-6</sub> alkyl, phenyl, -N(R<sup>51</sup>)R<sup>52</sup>-NH-C(O)-C<sub>1-6</sub> alkyl, -N(C<sub>1-6</sub> alkyl)-C(O)-C<sub>1-6</sub> alkyl or -NH-S(O)<sub>0-2</sub>-C<sub>1-6</sub> alkyl),

-C(S)-C<sub>3-7</sub> cycloalkyl,

-C(S)-C<sub>1-6</sub> alkyl,

-C(O)-O-C<sub>1-6</sub> alkyl,

-(CH<sub>2</sub>)<sub>0-4</sub>-N(R<sup>53</sup>)-C(O)-R<sup>54</sup>,

-N(R<sup>53</sup>)-C(O)-O-R<sup>54</sup>,

-C(O)-aryl (the said aryl may be substituted with halogen),

-C(O)-heteroaromatic ring,

-C(O)-aliphatic hetero ring,

hetero ring (the said hetero ring may be substituted with -C<sub>1-6</sub> alkyl (the said -C<sub>1-6</sub> alkyl may be substituted with halogen or -O-C<sub>1-6</sub> alkyl),

phenyl (the said phenyl may be substituted with halogen, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl),

halogen, CN, formyl, COOH, amino, oxo, hydroxy, hydroxy amidino or nitro,

R<sup>51</sup> and R<sup>52</sup> each independently denote hydrogen atom, -C<sub>1-6</sub> alkyl,

or 4-7 membered hetero ring formed by linking nitrogen atom, R<sup>51</sup> and R<sup>52</sup> together,

R<sup>53</sup> denotes a hydrogen atom or -C<sub>1-6</sub> alkyl,

$R^{54}$  denotes  $-C_{1-6}$  alkyl or,

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of  $R^{53}$  and  $R^{54}$ , and  $-N-C(O)-$  together or

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of  $R^{53}$  and  $R^{54}$ , and  $-N-C(O)-O-$  together (the said aliphatic hetero ring may be substituted with oxo, and moreover, the said aliphatic hetero ring may contain 1 or 2 double bonds in the ring),

$X_5$  denotes  $-O-$ ,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ , single bond or  $-O-C_{1-6}$  -alkyl",

$a$  denotes, each independently, an integer of 1, 2 or 3,

$q$  denotes an integer of 0-2,

$m$  denotes an integer of 0-2]

(wherein the following cases were excluded:

the case wherein one of  $X_5$  is  $-O-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ , and the other  $X_5$  is single bond, and also  $R^1$  is aryl or nitrogen-containing aromatic heteroring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said aryl may be substituted with 1-3  $R^4$ ),

the case wherein both  $X^5$  are single bonds, or

the case wherein both  $R^1$  are aliphatic heteroring).

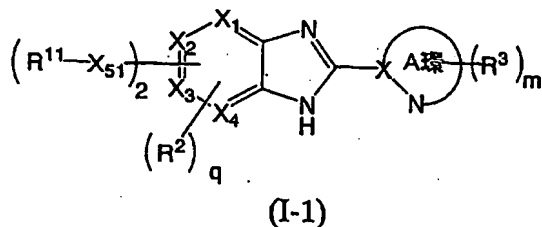
Moreover, this invention also relates to the following:

(2) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein in formula (I-0),  $X_1$  to  $X_4$  are all carbon atoms, or

(3) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein in formula (I-0),  $X_5$  is  $-O-$ ,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$  or single bond.

Moreover, this invention also relates to the following:

(4) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein the compound represented by formula (I-0) is the formula (I-1)



[in the formula,  $R^{11}$  denotes phenyl which may be substituted with 1-3  $R^4$  or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ), and also

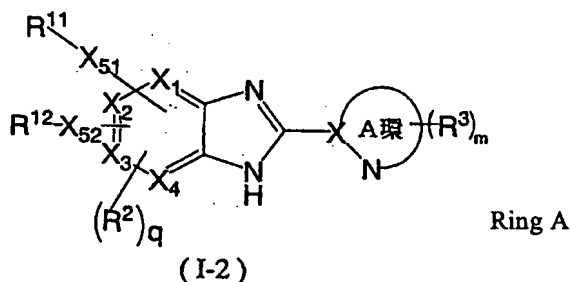
$X_{51}$  denotes  $-O-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ , and the other symbols are the same as above].

Moreover, this invention also relates to the following:

- (5) a compound in accordance with aforesaid (4) or pharmacologically acceptable salts thereof, wherein in formula (I-1), both  $R^{11}$  are phenyl which may be substituted with 1-3  $R^4$ , or
- (6) a compound in accordance with aforesaid (4) or pharmacologically acceptable salts thereof, wherein in formula (I-1), both  $R^{11}$  are 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ), or
- (7) a compound in accordance with aforesaid (4) or pharmacologically acceptable salts thereof, wherein in formula (I-1), one of the  $R^{11}$  is phenyl which may be substituted with 1-3  $R^4$  and also the other  $R^{11}$  is 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ).

Furthermore, this invention also relates to the following:

- (8) a compound in accordance with aforesaid (1) or pharmacologically acceptable salts thereof, wherein the compound represented by formula (I-0) is the formula (I-2)



[in the formula,  $R^{11}$  denotes phenyl which may be substituted with 1-3  $R^4$  or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ),

$R^{12}$  denotes 4 to 7-membered nitrogen-containing heteroring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said  $R^{12}$  may be substituted with 1-3  $R^4$ , and moreover, when the said hetero ring is an aliphatic hetero ring, it may contain 1 or 2 double bonds),

$X_{51}$  is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-,

$X_{52}$  is -O-, -S-, -S(O)-, -S(O)<sub>2</sub>- or single bond, and the other symbols are the same as above].

Moreover, this invention also relates to the following:

- (9) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2),  $R^{12}$  is 4 to 7-membered nitrogen-containing saturated aliphatic hetero

ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3  $R^4$ ) and also  $X_{52}$  is a single bond, or

$R^{12}$  is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid  $R^4$ ) and also  $X_{52}$  is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-,

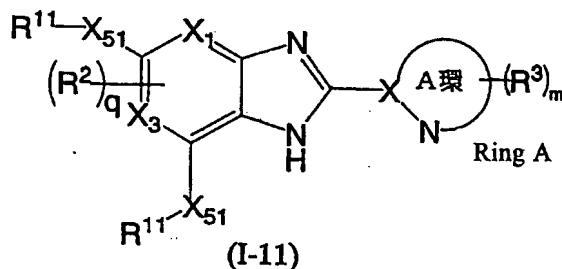
(10) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2),  $R^{12}$  is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3  $R^4$ ) and also  $X_{52}$  is a single bond, or

(11) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2),  $R^{12}$  is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid  $R^4$ ) and also  $X_{52}$  is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-,

(12) a compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2),  $R^{12}$  is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid  $R^4$ ) and also  $X_{52}$  is -O-.

Moreover, this invention also relates to the following:

(13) a compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-11)



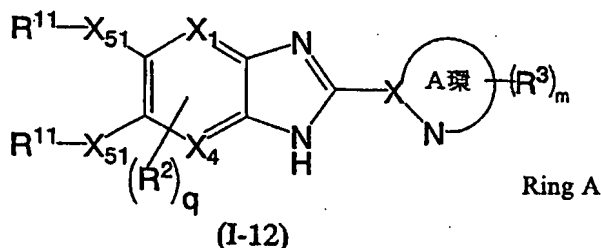
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(14) a compound in accordance with aforesaid (13) or pharmacologically acceptable salts thereof, wherein in formula (I-12), both  $X_{51}$  are -O-,

(15) ) a compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-12)

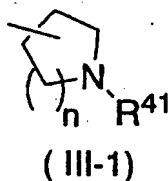


(each symbol is the same as above),

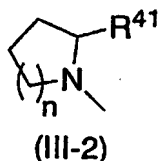
(16) a compound in accordance with aforesaid (15) or pharmacologically acceptable salts thereof, wherein in formula (I-12), both  $X_{51}$  are -O-.

Moreover, this invention also relates to the following:

(17) a compound in accordance with aforesaid (10) or pharmacologically acceptable salts thereof, wherein  $R^{12}$  in formula (I-2) is formula (III-1)



or formula (III-2)



[wherein, n denotes an integer of 1-3, and  $R^{41}$  denotes the group same as the aforesaid  $R^4$ ].

Moreover, this invention also relates to the following:

(18) a compound in accordance with any one of aforesaid (1) to (17) or pharmacologically acceptable salts thereof, wherein the A ring is thiazolyl, imidazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, pyrazolyl or pyrimidinyl which may be substituted with 1-3 of aforesaid  $R^4$ .

Moreover, this invention also relates to the following:

(19) a compound or pharmacologically acceptable salts thereof, wherein the compound

represented by formula (I-0) is

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole,  
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole,  
5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,6-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-cyanopyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-

benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,

5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole,

5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2-fluoro-phenoxy)-2-(pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole,

4-(2-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2,3-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

4-(2,5-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,

4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,

1-(2-(6-(5-bromo-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide,

2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile,

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylamino-ethanone,

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,

N-(5-(6-[1-acetyl-pyrrolidin-2-yl]-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide,

1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,



N-(2-(2-[6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl]-pyrrolidin-1-yl)-2-oxo-ethyl)-acetamide,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • mono trifluoroacetate,  
1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridine-2(1H)-one,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
(2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(1-acetyl-3-fluoropyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(6-(methoxymethylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol,  
2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide,  
5'-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one,  
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetyl-3-fluoropyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)

oxy)-2-pyridin-2-yl-1H-benzimidazole,  
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy)  
phenyl)-1,3-oxazolidin-2-one,  
6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl)  
oxy)-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)  
oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl)  
phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzi  
midazole,  
N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)  
pyrrolidin-1-yl)-2-oxo ethanamine,  
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl)  
oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-et  
hanone,  
1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-  
2-yl)-ethanone,  
1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl  
)-ethanone, or  
1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrro  
lidin-2-yl)-ethanone.

Moreover, this invention also relates to the following:

(20) a medicinal composition comprising the following (1)-(3) to be used for therapy, prevention  
and/or delay of onset of type II diabetes mellitus;

- (1) a compound in accordance with any one of the said (1) to (19),
- (2) a compound of 1 or 2 or more, selected from the group comprising following (a)-(h),
  - (a) other glucokinase activator,
  - (b) bis-guanide,
  - (c) PPAR agonist,
  - (d) insulin,
  - (e) somatostatin,
  - (f)  $\alpha$ -glucosidase inhibitor,
  - (g) insulin, and
  - (h) DPF-IV (dipeptidyl peptidase IV) inhibitor

- (3) a pharmacologically acceptable carrier,
- (21) a glucokinase activator containing as effective ingredient a compound in accordance with any one of the said (1) to (19) or pharmacologically acceptable salts thereof,
- (22) a therapeutic and/or preventive agent of diabetes mellitus containing as effective ingredient a compound in accordance with any one of the said (1) to (20) or pharmacologically acceptable salts thereof, or
- (23) a therapeutic and/or preventive agent of obesity containing as effective ingredient a compound in accordance with any one of the said (1) to (20) or pharmacologically acceptable salts thereof.

#### Ideal form for Carrying Out the Invention

Below the meanings of the terms used in this specification are explained, and the compounds in accordance with this invention are described in further detail.

In this specification, as following group, the species listed below can be nominated unless specified in particular.

As "aryl", hydrocarbon aromatic ring of carbon number 6-14 is meant preferably, and for example phenyl, naphthyl, biphenyl, anthryl and the like are proposed, among these, phenyl, naphthyl or biphenyl are preferred, and phenyl is more preferred.

As "C<sub>1-6</sub> alkyl", C<sub>1-6</sub> alkyl containing straight chain or divergence is denoted, and for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, neopentyl, isopentyl, 1,1-dimethylpropyl, 1-methyl butyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methyl pentyl, 2-methyl pentyl, 3-methyl pentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethyl butyl, 1,3-dimethyl butyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethyl butyl, 2-ethyl butyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and the like may be proposed.

As "C<sub>2-6</sub> alkenyl", C<sub>2-6</sub> alkenyl having a straight or branched chain is denoted, and for example, allyl, 2-propenyl, 1-butenyl, 2-butenyl, 2-methyl-2-butenyl, 1-pentenyl and the like may be proposed.

As "C<sub>3-7</sub> cycloalkyl", for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like may be proposed.

As "halogen", fluorine, chlorine, bromine or iodine is denoted.

As " $-(\text{CH}_2)_{1-6}\text{-OH}$ ", hydroxymethylene, hydroxy ethylene and the like may be proposed.

As " $-\text{O}-\text{C}_{1-6}$  alkyl", for example, methoxy, ethoxy, propoxy or tert butoxy and the like may be proposed.

As " $-(\text{CH}_2)_{1-6}\text{OC}_{1-6}$  alkyl", methoxymethyl, methoxyethyl, propyloxy methyl, isopropyl oxymethyl and the like may be proposed.

As, " $-\text{C}(\text{O})_{1-6}$  alkyl", acetyl, ethyl carbonyl, isopropyl carbonyl, propyl carbonyl and the like may be proposed.

As " $-\text{C}(\text{O})\text{OC}_{1-6}$  alkyl", for example, methoxycarbonyl, ethoxycarbonyl or tert butoxycarbonyl and the like may be proposed.

As " $-(\text{CH}_2)_{1-6}\text{-NH}_2$ ", aminomethyl, aminoethyl, aminopropyl and the like may be proposed.

As " $-\text{NH}-\text{C}_{1-6}$  alkyl", for example, methylamino, ethylamino, propylamino or 2-methyl butyl-amino and the like may be proposed.

As " $-\text{N-di}-(\text{C}_{1-6}$  alkyl)", it is meant a group in which the same or different aforesaid definition of " $\text{C}_{1-6}$  alkyl" and N are linked, and for example dimethylamino, ethyl propylamino, 2-methyl butyl-1-methylamino and the like may be proposed. Moreover, the same or different  $\text{C}_{1-6}$  alkyl in the " $-\text{N-di}-(\text{C}_{1-6}$  alkyl)" may form a ring together with nitrogen atom, and for example piperidine, pyrrolidine and the like are nominated as embodiment of the said ring.

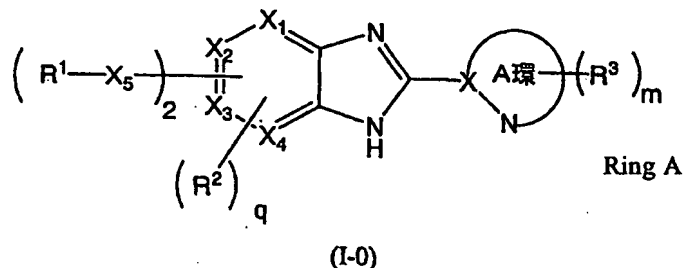
" $-\text{CH}_3\text{-F}_a$ " means a group in which the 1-3 hydrogen atoms in methyl are substituted by fluorine atom, and for example, trifluoromethyl, difluoromethyl or fluoromethyl and the like may be proposed.

" $-\text{OCH}_3\text{-F}_a$ " denotes a group in which oxygen atom is combined with " $-\text{CH}_3\text{-F}_a$ " of the said definition, and for example trifluoromethoxy, difluoromethoxy or fluoromethoxy and the like may be proposed.

The a denotes an integer of 1-3.

In order to disclose further using examples of compounds in accordance with this invention, various notations used in formula (I-0), (I-1), (I-2), (I-11) or (I-12) will be explained with examples.

The compound represented by formula (I-0) in accordance with this invention will be explained.



X<sub>5</sub> denotes -O-, -S-, -S(O)-, -S(O)<sub>2</sub>-, single bond or -O-C<sub>1-6</sub>-alkyl.

R<sup>1</sup> denotes aryl or a 4-10 membered monocyclic or bicyclic nitrogen-containing heterorings containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring.

As "aryl" of the R<sup>1</sup>, the same aryl as the aforesaid definition may be proposed, and phenyl, naphthyl or biphenyl are preferred, and phenyl is more preferred.

As "4-7 membered monocyclic or 9 or 10 membered condensed heteroring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring" of the R<sup>1</sup>, it is meant a monocycle of 4- 7- membered ring as the ring or 9- or 10-memebred bicyclic ring of aliphatic hetero ring or aromatic hetero ring wherein 1 to 4 of the ring constituting atoms are heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and the other atoms of the hetero ring constituting ring are carbon atoms.

When nitrogen atom is contained in the said hetero ring, said nitrogen atom may form N-oxide.

When 2 or 3 heteroatoms are present in the said hetero ring, these may be the same or different.

When the said hetero ring is aliphatic hetero ring, moreover, the methylene in the said hetero ring may be replaced with nitrogen atom, sulfur atom or oxygen atom, furthermore, the said sulfur atom may be oxidized to form sulphenyl or sulfonyl.

As said hetero ring, for example, azetidiny, thiazolidiny, pyrrolidiny, pyrroliny, 2-pyrrolidonyl, azepany, 2,5-dioxo pyrrolidiny, 2-benzoxolinonyl, 1,1-dioxo tetrahydrothienyl, 2,4-dioxo imidazolidiny, 2-oxo-[1,3,4]-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodioxoly, [1,2,4]-oxadiazolinyl, 2-azabicyclo [2.2.1] heptyl, 4-thiazolidonyl,

morpholinino, 2-oxo tetrahydrofuranyl, tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, isoxazolyl, tetrahydropyranyl, piperidyl, 1-oxo-1,3-dihydroiso indolyl, piperazinyl, thiomorpholino, 1,1-dioxo thiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiazolyl, thiadiazolyl, isothiazolyl, [1,2,4]-triazolyl, [1,2,3]-triazolyl, pyranyl, indolyl, pyrimidinyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl or iso quinolynyl may be proposed.

Among these, as 4-7 membered monocyclic hetero ring, for example, azetidiny, isoxazolyl, pyrrolidinyl, 2-pyrrolidonyl, 2,5-dioxo pyrrolidonyl, morpholino, tetrahydrofuranyl, azepanyl, piperidyl, piperazinyl, thiomorpholino, tetrahydropyranyl, imidazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyrazolyl, indolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyridazinyl, pyridyl and the like may be proposed.

Among these, as 4-7 membered monocyclic aliphatic hetero ring, for example, azetidiny, pyrrolidinyl, piperidyl, piperidinyl, azepanyl, piperazinyl, morpholino, thiomorpholino, homopiperazinyl, imidazolidinyl, pyrazolidinyl and the like may be proposed.

Among these, as 5 or 6 membered monocyclic heteroaromatic ring, for example, pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and the like may be proposed.

Among these, 9 or 10 membered condensed hetero ring, for example benzofuranyl, benzimidazolyl, benzothiophenyl, benzothiazolyl, benzo isothiazolyl, benzoxazolyl, benzo isoxazolyl, pyrido imidazolyl, quinolyl, isoquinolyl, quinoxaliny, quinazolinyl, phthalidinyl, cinnolinyl, indolyl, indazolyl, purinyl, indoliziny, isoindolyl, pteridinyl, naphthyridinyl and the like are proposed.

As the said hetero ring, 4-7 membered monocyclic aliphatic hetero ring in which the at least one of the said hetero ring constituting atom is nitrogen atom or 5 or 6 membered heteroaromatic ring is preferred.

R<sup>1</sup> may be substituted with 1-3 R<sup>4</sup>.

Wherein, R<sup>4</sup> each independently denotes

- C<sub>1-6</sub> alkyl (the said alkyl may be substituted with the same or different 1 to 3 hydroxy, halogen,
- OC(O)-C<sub>1-6</sub> alkyl (the said alkyl may be substituted with 1 to 3 halogen), or -OC<sub>1-6</sub> alkyl)
- C<sub>3-8</sub> cycloalkyl,
- C<sub>2-6</sub> alkenyl,

$-\text{C}(\text{O})-\text{N}(\text{R}^{51})\text{R}^{52}$ ,  
 $-\text{S}(\text{O})_2-\text{N}(\text{R}^{51})\text{R}^{52}$ ,  
 $-\text{O}-\text{C}_{1-6}$  alkyl (the said  $\text{C}_{1-6}$  alkyl may be substituted with halogen or  $\text{N}(\text{R}^{51})\text{R}^{52}$ ),  
 $-\text{S}(\text{O})_{0-2}-\text{C}_{1-6}$  alkyl,  
 $-\text{C}(\text{O})-\text{C}_{1-6}$  alkyl (the said  $\text{C}_{1-6}$  alkyl may be substituted with halogen, amino, CN, hydroxy,  $-\text{O}-\text{C}_{1-6}$  alkyl,  $-\text{CH}_3-\text{F}$ ,  $-\text{OC}(\text{O})-\text{C}_{1-6}$  alkyl,  $-\text{N}(\text{C}_{1-6} \text{ alkyl})\text{C}(\text{O})\text{O}-\text{C}_{1-6}$  alkyl,  $-\text{NH}-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$  alkyl, phenyl,  $-\text{N}(\text{R}^{51})\text{R}^{52}-\text{NH}-\text{C}(\text{O})-\text{C}_{1-6}$  alkyl,  $-\text{N}(\text{C}_{1-6} \text{ alkyl})-\text{C}(\text{O})-\text{C}_{1-6}$  alkyl or  $-\text{NH}-\text{S}(\text{O})_{0-2}-\text{C}_{1-6}$  alkyl),  
 $-\text{C}(\text{S})-\text{C}_{3-7}$  cycloalkyl,  
 $-\text{C}(\text{S})-\text{C}_{1-6}$  alkyl,  
 $-\text{C}(\text{O})-\text{O}-\text{C}_{1-6}$  alkyl,  
 $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}^{53})-\text{C}(\text{O})-\text{R}^{54}$ ,  
 $-\text{N}(\text{R}^{53})-\text{C}(\text{O})-\text{O}-\text{R}^{54}$ ,  
 $-\text{C}(\text{O})-\text{aryl}$  (the said aryl may be substituted with halogen),  
 $-\text{C}(\text{O})-\text{heteroaromatic ring}$ ,  
 $-\text{C}(\text{O})-\text{aliphatic hetero ring}$ ,  
hetero ring (the said hetero ring may be substituted with  $-\text{C}_{1-6}$  alkyl (the said  $-\text{C}_{1-6}$  alkyl may be substituted with halogen or  $-\text{O}-\text{C}_{1-6}$  alkyl),  
phenyl (the said phenyl may be substituted with halogen,  $-\text{C}_{1-6}$  alkyl,  $-\text{O}-\text{C}_{1-6}$  alkyl),  
halogen, CN, formyl, COOH, amino, oxo, hydroxy, hydroxy amidino or nitro.

As "halogen" of  $\text{R}^4$  denotes the same group as in the aforesaid definition.

As " $-\text{C}_{1-6}$  alkyl" of  $\text{R}^4$  denotes an alkyl of carbon number 1-6 having straight chain or branching, and for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, neopentyl, isopentyl, 1,1-dimethylpropyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methyl pentyl, 2-methyl pentyl, 3-methyl pentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethyl butyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethyl butyl, 1-ethyl butyl, 2-ethyl butyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and the like may be proposed.

The said " $-\text{C}_{1-6}$  alkyl" may be substituted with 1-3 hydroxy, halogen,  $-\text{OC}(\text{O})-\text{C}_{1-6}$  alkyl (the said alkyl may be substituted with 1-3 halogen ) or  $-\text{O}-\text{C}_{1-6}$  alkyl.

When the said " $\text{C}_{1-6}$  alkyl" contains 2 or 3 of the aforesaid substituent, these may be the same or different.

As halogen of said substituent, the same group as in the aforesaid definition may be proposed.

As  $-OC(O)-C_{1-6}$  alkyl of said substituent, for example, methylcarbonyloxy, ethylcarbonyloxy, isopropylcarbonyloxy and the like may be proposed.

The  $-OC(O)-C_{1-6}$  alkyl of said substituent may be substituted with 1-3 halogen atoms of the aforesaid definition.

As  $-O-C_{1-6}$  alkyl of said substituent, for example, methoxy, ethoxy, propoxy, isopropoxy and the like may be proposed.

The " $-S(O)_{0-2}-C_{1-6}$  alkyl" denoted by  $R^4$  means a group in which the  $C_{1-6}$  alkyl of the said definition is combined with  $-S(O)_{0-2}-$ , and for example  $-S$ -ethyl,  $-S$ -methyl,  $-S$ -isopropyl,  $-S$ -propyl,  $-S(O)_2$ -methyl,  $-S(O)_2$ -ethyl and the like may be proposed.

The  $C_{1-6}$  alkyl in said " $-S(O)_{0-2}-C_{1-6}$  alkyl" may be substituted with hydroxy.

As " $-C_{3-8}$  cycloalkyl" of  $R^4$ , the same groups as in the aforesaid definition may be proposed.

As " $-C_{2-6}$  alkenyl" of  $R^4$ , the same groups as in the aforesaid definition may be proposed.

The " $C(O)N(R^{51})R^{52}$ " of  $R^4$ , means a substituted or unsubstituted carbamoyl group, or a group in which carbonyl and 4-7 membered aliphatic hetero ring formed by linking N,  $R^{51}$  and  $R^{52}$  together.

Among the " $C(O)N(R^{51})R^{52}$ " of  $R^4$ , as the substituted carbamoyl which is substituted or unsubstituted, for example, carbamoyl, methyl carbamoyl, ethyl carbamoyl, isopropyl carbamoyl, propyl carbamoyl, ethyl methyl carbamoyl, dimethyl carbamoyl, isopropyl methyl carbamoyl, diisopropyl carbamoyl, diethyl carbamoyl and the like may be proposed.

Among the " $C(O)N(R^{51})R^{52}$ " of  $R^4$ , as the 4-7 membered aliphatic group, for example, azetidiny, pyrrolidinyl, piperidino, piperazinyl, morpholino and the like may be proposed. Accordingly, as  $C(O)N(R^{51})R^{52}$ , azetidine-1-carbonyl, pyrrolidine-1-carbonyl, piperidine-1-carbonyl, piperazine-1-carbonyl, morpholine-1-carbonyl and the like may be proposed.

As " $-C(O)-O-C_{1-6}$  alkyl" of  $R^4$ , the same group as in " $-C(O)-O-C_{1-6}$  alkyl" of the said definition may be proposed.

As " $-O-C_{1-6}$  alkyl" of  $R^4$ , the same group as in " $-O-C_{1-6}$  alkyl" of the said definition may be



proposed.

The said -O-C<sub>1-6</sub> alkyl may be substituted with halogen or N(R<sup>51</sup>)R<sup>52</sup>.

As "-C(O)-C<sub>1-6</sub> alkyl" of R<sup>4</sup>, the same group as in "-C(O)-C<sub>1-6</sub> alkyl" of the said definition may be proposed.

The said "-C(O)-C<sub>1-6</sub> alkyl" may be substituted with halogen, amino, -CH<sub>3-a</sub>F<sub>a</sub>, CN, hydroxy, -O-C<sub>1-6</sub> alkyl, -O-C(O)-C<sub>1-6</sub> alkyl, -N-(C<sub>1-6</sub> alkyl)-C(O)O-C<sub>1-6</sub> alkyl, -NH-C(O)O-C<sub>1-6</sub> alkyl, phenyl, -N(R<sup>51</sup>)R<sup>52</sup>-NH-C(O)-C<sub>1-6</sub> alkyl, -N-(C<sub>1-6</sub> alkyl)-C(O)-C<sub>1-6</sub> alkyl or -NH-S(O)<sub>0-2</sub>-C<sub>1-6</sub> alkyl.

As "halogen" of the said substituent, the same group as in halogen of the said definition may be proposed.

As "-CH<sub>3-a</sub>F<sub>a</sub>" of the said substituent, the same group as in "-CH<sub>3-a</sub>F<sub>a</sub>" of the said definition may be proposed.

As "-O-C<sub>1-6</sub> alkyl" of the said substituent, the same group as in "-O-C<sub>1-6</sub> alkyl" of the said definition may be proposed.

As "-O-C(O)-C<sub>1-6</sub> alkyl" of the said substituent, the same group as in the said "-O-C(O)-C<sub>1-6</sub> alkyl" may be proposed.

The "-N-(C<sub>1-6</sub> alkyl)-C(O)O-C<sub>1-6</sub> alkyl" of the said substituent means a group in which the said -C(O)O-C<sub>1-6</sub> alkyl is combined with -N-(C<sub>1-6</sub> alkyl)-, and for example -N(Me)-C(O)O-tert-butyl and the like may be proposed.

The "-NH-C(O)O-C<sub>1-6</sub> alkyl" of the said substituent means a group in which the said -C(O)O-C<sub>1-6</sub> alkyl is combined with -NH-, and for example, -NH-C(O)O-methyl, -NH-C(O)O-ethyl, -NH-C(O)O-isopropyl-NH-C(O)-propyl and the like may be proposed.

As "-N(R<sup>51</sup>)R<sup>52</sup>" of the said substituent, the same group as in the said "-N(R<sup>51</sup>)R<sup>52</sup>" may be proposed.

The "-NH-C(O)-C<sub>1-6</sub> alkyl" of said substituent means a group in which -NH-C(O)- and the aforesaid -C<sub>1-6</sub> alkyl are combined, and for example, -NH-C(O)-methyl, -NH-C(O)-ethyl, -NH-C(O)-isopropyl, -NH-C(O)-propyl and the like may be proposed.

The "-N-(C<sub>1-6</sub> alkyl)-C(O)-C<sub>1-6</sub> alkyl" of said substituent means a group in which C<sub>1-6</sub> alkyl of the said definition is combined with -N-(C<sub>1-6</sub> alkyl-C(O)-, and for example, -N(methyl)-C(O)-methyl, -N(methyl)-C(O)-ethyl, -N(ethyl)-C(O)-isopropyl, -N(methyl)-C(O)-isopropyl, -N(isopropyl)-C(O)-methyl and the like may be proposed.

The NH-S(O)<sub>0-2</sub>-C<sub>1-6</sub> alkyl of said substituent denotes a group in which the said -S(O)<sub>0-2</sub>-C<sub>1-6</sub> alkyl is combined with -NH-, and for example -NH-S(O)<sub>2</sub>-methyl, -NH-S(O)<sub>2</sub>-ethyl, -NH-S(O)<sub>2</sub>-isopropyl and the like may be proposed.

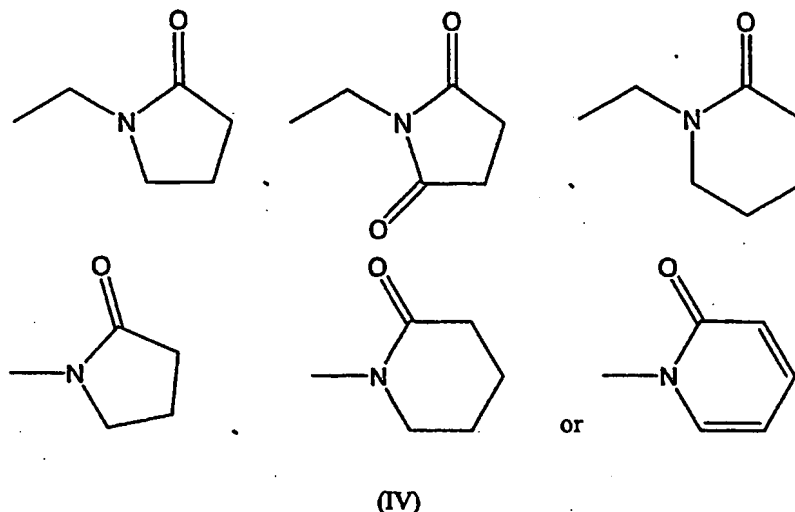
As "-C(O)-C<sub>1-6</sub> alkyl" that may contain on the said substituent on 1-6C alkyl, for example, fluoromethyl carbonyl, 2,2,2-trifluoroethyl carbonyl, cyanomethyl carbonyl, hydroxymethyl carbonyl, 2-hydroxyethyl carbonyl, methoxymethyl carbonyl, aminomethyl carbonyl, N-methylamino carbonyl, 2-phenylethyl carbonyl and the like may be proposed.

The "-C(S)-C<sub>1-6</sub> alkyl" of R<sup>4</sup> denotes a group in which "-C<sub>1-6</sub> alkyl" of the said definition is combined with -C(S)-, and for example, -C(S)-methyl, -C(S)-ethyl, -C(S)-isopropyl, -C(S)-propyl and the like may be proposed.

In "-(CH<sub>2</sub>)<sub>0-4</sub>-N(R<sup>53</sup>)-C(O)-R<sup>54</sup>" of R<sup>4</sup>, ring R<sup>53</sup> denotes a hydrogen atom or C<sub>1-6</sub> alkyl, R<sup>54</sup> denotes C<sub>1-6</sub> alkyl or in the -N(R<sup>53</sup>)-C(O)-R<sup>54</sup> of the "-(CH<sub>2</sub>)<sub>0-4</sub>-N(R<sup>53</sup>)-C(O)-R<sup>54</sup>", -N-C(O)- and alkyl of R<sup>53</sup> and R<sup>54</sup> are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring (the said hetero ring may be substituted with oxo, and moreover 1 or 2 double bonds may be contained in the ring).

As "-(CH<sub>2</sub>)<sub>0-4</sub>-N(R<sup>53</sup>)-C(O)-R<sup>54</sup>" when R<sup>53</sup> is hydrogen atom or -C<sub>1-6</sub> alkyl and R<sup>54</sup> is -C<sub>1-6</sub> alkyl, for example, -CH<sub>2</sub>-NH-C(O)-methyl, -CH<sub>2</sub>-NH-C(O)-ethyl, -CH<sub>2</sub>-NH-C(O)-isopropyl, -CH<sub>2</sub>-NH-C(O)-propyl, -CH<sub>2</sub>-N(methyl)-C(O)-methyl, -CH<sub>2</sub>-N(ethyl)-C(O)-methyl, -NH-C(O)-methyl, -NH-C(O)-ethyl, -NH-C(O)-isopropyl, -NH-C(O)-propyl, -N(methyl)-C(O)-methyl, -N(ethyl)-C(O)-methyl and the like may be proposed.

As "-(CH<sub>2</sub>)<sub>0-4</sub>-N(R<sup>53</sup>)-C(O)-R<sup>54</sup>" when -N-C(O)- and alkyl of R<sup>53</sup> and R<sup>54</sup> are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring (the said hetero ring may be substituted with oxo, and moreover 1 or 2 double bonds may be contained in the ring), for example, groups represented by formula

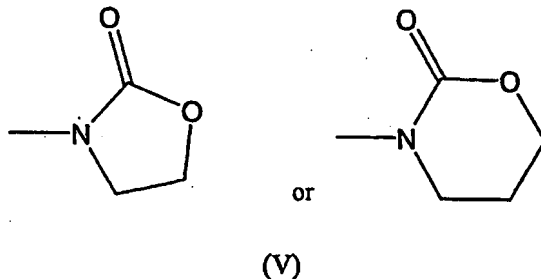


or the like may be proposed.

In " $-N(R^{55})-C(O)-O-R^{56}$ " of  $R^4$ ,  $R^{55}$  denotes hydrogen atom or  $-C_{1-6}$  alkyl and  $R^{56}$  denotes  $-C_{1-6}$  alkyl, or in " $-N(R^{55})-C(O)-O-R^{56}$ " of the " $-N(R^{55})-C(O)-CO-R^{56}$ ",  $-N-C(O)-O-$  and  $R^{55}$  and  $R^{56}$  are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring.

As " $-N(R^{55})-C(O)-O-R^{56}$ " when  $R^{55}$  is hydrogen atom or  $-C_{1-6}$  alkyl and  $R^{56}$  is  $-C_{1-6}$  alkyl, for example,  $-NH-C(O)-O$ -methyl,  $-NH-C(O)-O$ -ethyl,  $-NH-C(O)-CO$ -isopropyl,  $-NH-C(O)-CO$ -propyl,  $-N$ (methyl)- $C(O)-O$ -methyl,  $-N$ (ethyl)- $C(O)-O$ -methyl and the like may be proposed.

As " $-N(R^{55})-C(O)-O-R^{56}$ " when  $-N-C(O)-O-$  and  $R^{55}$  and  $R^{56}$  are linked together to form 4-7 membered nitrogen-containing aliphatic hetero ring, for example, groups represented by formula (V)



or the like may be proposed.

The " $-C(O)$ -aryl" of  $R^4$  means a group in which the aryl of the said definition denotes is combined with carbonyl, and for example benzoyl, naphthyl carbonyl and the like may be proposed.

Moreover, the aryl in said "-C(O)-aryl" may be substituted with 1-3 halogen atoms of the said definition.

When 2 or 3 of the said halogens of said substituents are present, these may be the same or different.

The "-C(O)-heteroaromatic ring" of  $R^4$  means a group in which carbonyl is combined with 5 or 6 membered monocyclic heteroaromatic ring or 9 or 10 membered bicyclic heteroaromatic ring of the said definition, and for example, -C(O)-pyrrolyl, -C(O)-furyl, -C(O)-thienyl, -C(O)-C(O)-pyrazolyl, -C(O)-isoxazolyl, -C(O)-iso thiazolyl, -C(O)-imidazolyl, -C(O)-oxazolyl, -C(O)-thiazolyl, -C(O)-triazolyl, -C(O)-oxadiazolyl, -C(O)-thiadiazolyl, -C(O)-tetrazolyl, -C(O)-pyridyl, -C(O)-pyrazinyl, -C(O)-pyrimidinyl, -C(O)-pyridazinyl and the like may be proposed.

The "-C(O)-heteroaromatic ring" of  $R^4$  means a group in which carbonyl is combined with 4-7 membered monocyclic aliphatic hetero ring of the said definition, and for example, -C(O)-azetidiny, -C(O)-pyrrolidinyl, -C(O)-piperidine, -C(O)-piperidinyl, -C(O)-azepanyl, -C(O)-piperazinyl, -C(O)-morpholino, -C(O)-thiomorpholino, -C(O)-homopiperazinyl, -C(O)-imidazolidinyl, -C(O)-pyrazolidinyl and the like may be proposed.

As "hetero ring" of  $R^4$ , the same group as "hetero ring" of  $R^1$  may be proposed.

Moreover, the said hetero ring may be substituted with 1-3 of -C<sub>1-6</sub>-alkyl, halogen or -O-C<sub>1-6</sub>-alkyl.

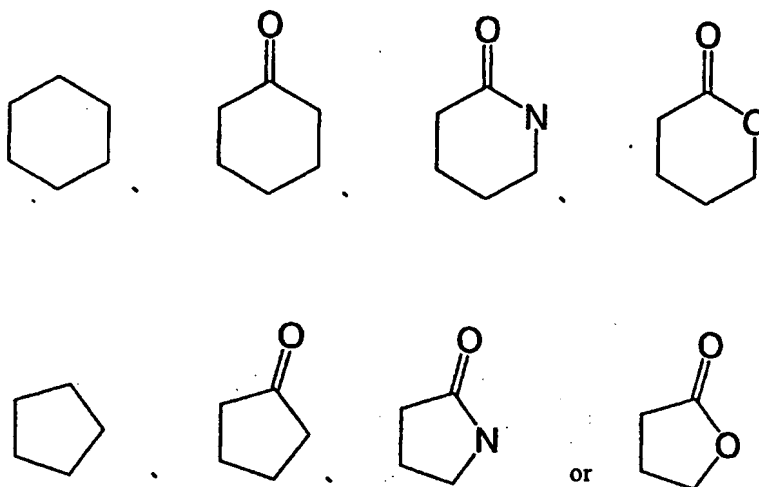
When 2 or 3 of the said substituent are present, these may be the same or different.

As the -C<sub>1-6</sub>-alkyl, halogen and -O-C<sub>1-6</sub>-alkyl of the said substituent, the groups same as in the groups defined as above may be proposed.

As "the halogen" of  $R^4$ , the same groups as in "halogen" of the said definition may be proposed.

The "phenyl" of  $R^4$  may be substituted with halogen, -C<sub>1-6</sub>-alkyl or -O-C<sub>1-6</sub>-alkyl.

When  $R^1$  has 2 or 3  $R^4$  as substituents, the two of the same or different  $R^4$  may be linked together, to form a 4-6 membered ring, and for example, groups represented by formula (VI)



(VI)

may be proposed.

-X5-denotes -O-, -S-, -S(O)-, -S(O)<sub>2</sub>-, single bond or -O-C<sub>1-6</sub>-alkyl.

As -X5-, -O-, -S-, -S(O)-, -S(O)<sub>2</sub>- or single bond is preferred.

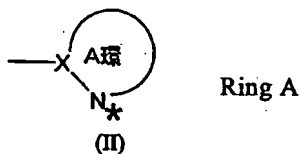
As R<sup>1</sup>-X<sub>5</sub>- (the said R<sup>1</sup> may be substituted with 1-3 of the aforesaid R<sub>4</sub>), for example, phenyl sulphonyl, phenoxy, benzyloxy, phenethyl oxy, 2-cyano phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 2-cyano-6-fluoro phenoxy, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-fluoro-6-carbamoyl phenoxy, 2-methylcarbamoyl phenoxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 2-methoxy-phenoxy, 3-methoxyphenoxy, 4-methoxyphenoxy, 4-methoxymethyl phenoxy, 2-isopropyl phenoxy, 3-isopropyl phenoxy, 4-isopropyl phenoxy, 2-methylphenoxy, 3-methylphenoxy, 4-methylphenoxy, 2-ethyl phenoxy, 3-ethyl phenoxy, 4-ethyl phenoxy, 2-acetyl phenoxy, 3-acetyl phenoxy, 4-acetyl phenoxy, 2-methanesulphonyl-phenoxy, 3-methanesulphonyl phenoxy, 3-chloro-4-methanesulphonyl phenoxy, 4-methanesulphonyl phenoxy, 2-ethanesulphonyl phenoxy, 3-ethanesulphonyl phenoxy, 4-ethanesulphonyl phenoxy, 2-methoxycarbonyl phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-ethoxycarbonyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-hydroxyphenoxy, 3-hydroxyphenoxy, 4-hydroxyphenoxy, 2-hydroxymethyl phenoxy, 3-hydroxymethyl phenoxy, 4-hydroxymethyl phenoxy, 2-hydroxyethyl phenoxy, 3-hydroxyethyl phenoxy, 4-hydroxyethyl phenoxy, 2-formyl phenoxy, 3-formyl phenoxy, 4-formyl phenoxy, 2-(1-hydroxyethyl) phenoxy, 3-(1-hydroxyethyl) phenoxy, 4-(1-hydroxyethyl) phenoxy, 2,3-difluoro phenoxy, 2,5-difluoro phenoxy, 2,4-difluoro phenoxy,

2,6-difluoro phenoxy, 2-fluoro phenoxy, 3-fluoro phenoxy, 4-fluoro phenoxy,  
 2-di-fluoromethoxyphenoxy, 3-di-fluoromethoxyphenoxy, 4-di-fluoromethoxyphenoxy,  
 2-trifluoromethoxyphenoxy, 3-trifluoromethoxyphenoxy, 4-trifluoromethoxyphenoxy,  
 2-(1H-tetrazol-5-yl) phenoxy, 3-(1H-tetrazol-5-yl) phenoxy, 4-(1H-tetrazol-5-yl) phenoxy,  
 4-(2-methyl-2H-tetrazol-5-yl) phenoxy, 2-(oxadiazol-3-yl) phenoxy, 3-(oxadiazol-3-yl) phenoxy,  
 4-(oxadiazol-3-yl) phenoxy, 2-(5-methyl oxadiazol-3-yl) phenoxy, 3-(5-methyl oxadiazol-3-yl)  
 phenoxy, 4-(5-methyl oxadiazol-3-yl) phenoxy, 2-methoxyphenyl sulphanyl, 3-methoxyphenyl  
 sulphanyl, 4-methoxyphenyl sulphanyl, 2-methoxyphenylmethyl sulphanyl,  
 3-methoxyphenylmethyl sulphanyl, 4-methoxyphenylmethyl sulphanyl  
 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4]  
 oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-(N-hydroxy  
 amidino) phenoxy, 3-(N-hydroxy amidino) phenoxy, 4-(N-hydroxy amidino) phenoxy,  
 2'-fluorobipheny-4-yloxy, pyridin-2-yl sulphanyl, pyridin-3-yl sulphanyl, pyridin-4-yl sulphanyl,  
 pyridin-4-yl sulfonyl aminopyridin-2-yloxy, pyridin-2-yloxy, pyridin-3-yloxy, pyridine-4-yloxy,  
 2-methoxypyridin-3-yloxy, 2-methoxypyridine-4-yloxy, 6-methoxypyridin-3-yloxy,  
 6-methoxypyridin-2-yloxy, 3-methoxypyridin-2-yloxy, 4-methoxypyridin-2-yloxy,  
 5-methoxypyridin-2-yloxy, 6-methoxymethyl pyridin-3-yloxy,  
 2-difluoromethoxypyridin-3-yloxy, 4-difluoromethoxypyridin-3-yloxy, 6-methylpyridin-2-yl  
 sulphanyl, 5-methylpyridin-2-yl sulphanyl, 4-methylpyridin-2-yl sulphanyl, 3-methylpyridin-2-yl  
 sulphanyl, 4-cyano-pyridin-3-yloxy, 6-cyano-pyridin-3-yloxy,  
 4-dimethylcarbamoyl-pyridin-3-yloxy, 6-methanesulphonyl-pyridin-3-yloxy,  
 6-ethanesulphonyl-pyridin-3-yloxy, 4-methanesulphonyl-pyridin-3-yloxy,  
 2-cyano-pyridin-3-yloxy, 2-dimethylcarbamoyl-pyridin-3-yloxy,  
 2-methanesulphonyl-pyridin-3-yloxy, 2-methylpyridin-3-yl sulphanyl, 2-chloropyridin-3-yloxy,  
 6-acetyl-amino-pyridin-3-yloxy, 2-oxo-2H-[1,3'] bipyridine-6'-yloxy, 4-methylpyridin-3-yl  
 sulphanyl, 5-methylpyridin-3-yl sulphanyl, 6-methylpyridin-3-yl sulphanyl, 2-methylpyridin-4-yl  
 sulphanyl, 3-methylpyridin-4-yl sulphanyl, 4-methylpyridin-3-yl sulfonyl, 5-methylpyridin-3-yl  
 sulfonyl, 6-methylpyridin-3-yl sulfonyl, 2-methylpyridin-3-yl sulfonyl, 3-methylpyridin-2-yl  
 sulfonyl, 4-methylpyridin-2-yl sulfonyl, 5-methylpyridin-2-yl sulfonyl, 6-methylpyridin-2-yl  
 sulfonyl, 2-oxo-1,2-dihydropyridin-3-yloxy, 1-methyl-2-oxo-1,2-dihydropyridin-3-yloxy,  
 1-ethyl-2-oxo-1,2-dihydropyridin-3-yloxy, 5-bromopyridin-2-yloxy, 6-(5-methyl-[1,2,4]  
 oxadiazol-3-yl-pyridine)-3-yloxy, 6-([1,2,4] oxadiazol-3-yl-pyridine)-3-yloxy, 1H-imidazol-2-yl  
 sulphanyl, 1-methyl-1H-imidazol-2-yl sulphanyl, 4H-[1,2,4] triazol-3-yl sulphanyl,  
 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl, 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yloxy,  
 5-(2-oxo-oxadiazolidin-3-yl) pyridin-2-yloxy, 6-pyrazin-2-yl-pyridin-3-yloxy, 1-acetyl  
 pyrrolidin-2-yl, 2-acetyl pyrrolidin-1-yl, 1-acetyl-3-fluoro-pyrrolidin-2-yl,  
 1-acetyl-5-methyl-pyrrolidin-2-yl, 1-acetyl piperidin-2-yl, 1-ethyl carbonyl-pyrrolidin-2-yl,  
 2-ethyl carbonyl pyrrolidin-1-yl, 1-ethyl carbonyl-piperidin-2-yl, 1-n-propyl

carbonyl-pyrrolidin-2-yl, 2-n-propyl carbonyl-pyrrolidin-2-yl, 1-n-propyl carbonyl-piperidin-2-yl,  
 1-isopropyl-pyrrolidin-2-yl, 2-isopropyl-pyrrolidin-1-yl, 1-isopropyl-piperidin-2-yl,  
 1-hydroxyethyl carbonyl-pyrrolidin-2-yl, 2-hydroxyethyl carbonyl-pyrrolidin-1-yl,  
 1-hydroxyethyl carbonyl-piperidin-2-yl, 1-hydroxymethyl carbonyl-pyrrolidin-2-yl,  
 2-hydroxymethyl carbonyl-pyrrolidin-1-yl, 1-hydroxymethyl carbonyl-piperidin-2-yl,  
 1-methoxymethyl carbonyl-pyrrolidin-2-yl, 2-methoxymethyl carbonyl-pyrrolidin-1-yl,  
 1-methoxymethyl carbonyl-piperidin-2-yl, 1-ethoxymethyl carbonyl-pyrrolidin-2-yl,  
 2-ethoxymethyl carbonyl-pyrrolidin-1-yl, 1-ethoxymethyl carbonyl-piperidin-2-yl,  
 1-methylpyrrolidin-2-yl, 2-methylpyrrolidin-1-yl, 1-methylpiperidin-2-yl, 1-ethylpyrrolidin-2-yl,  
 2-ethylpyrrolidin-1-yl, 1-ethylpiperidin-2-yl, 1-phenyl carbonyl-pyrrolidin-2-yl, 2-phenyl  
 carbonyl-pyrrolidin-1-yl, 1-phenyl carbonyl-piperidin-2-yl, 1-phenethyl carbonyl-pyrrolidin-2-yl,  
 2-phenethyl carbonyl-pyrrolidin-1-yl, 1-phenethyl carbonyl-piperidin-2-yl, 1-benzyl  
 carbonyl-pyrrolidin-2-yl, 2-benzyl carbonyl-pyrrolidin-1-yl, 1-benzyl carbonyl-piperidin-2-yl,  
 1-dimethylaminomethyl carbonyl-pyrrolidin-2-yl, 2-dimethylaminomethyl  
 carbonyl-pyrrolidin-1-yl, 1-dimethylaminomethyl carbonyl-piperidin-2-yl, 1-methylaminomethyl  
 carbonyl-pyrrolidin-2-yl, 2-methylaminomethyl carbonyl-pyrrolidin-1-yl, 1-methylaminomethyl  
 carbonyl-piperidin-2-yl, 1-cyclohexyl carbonyl-pyrrolidin-2-yl, 2-cyclohexyl  
 carbonyl-pyrrolidin-1-yl, 1-cyclohexyl carbonyl-piperidin-2-yl, 1-cyclopentyl  
 carbonyl-pyrrolidin-2-yl, 2-cyclopentyl carbonyl-pyrrolidin-1-yl, 1-cyclopentyl  
 carbonyl-piperidin-2-yl, 1-(1-methyl-3-oxobutyl carbonyl)-pyrrolidin-2-yl,  
 2-(1-methyl-3-oxobutyl carbonyl)-pyrrolidin-1-yl, 1-(1-methyl-3-oxo butyl  
 carbonyl)-piperidin-2-yl, 1-methanesulphonyl-pyrrolidin-2-yl,  
 2-methanesulphonyl-pyrrolidin-1-yl, 1-methanesulphonyl-piperidin-2-yl,  
 1-ethanesulphonyl-pyrrolidin-2-yl, 2-ethanesulphonyl-pyrrolidin-1-yl,  
 1-ethanesulphonyl-piperidin-2-yl, 1-isopropyl sulfonyl-pyrrolidin-2-yl, 2-isopropyl  
 sulfonyl-pyrrolidin-1-yl, 1-isopropyl sulfonyl-piperidin-2-yl, 1-carbamoyl-pyrrolidin-2-yl,  
 2-carbamoyl-pyrrolidin-1-yl, 1-carbamoyl-piperidin-2-yl, 1-carbamoylmethyl-pyrrolidin-2-yl,  
 2-carbamoylmethyl-pyrrolidin-1-yl, 1-carbamoylmethyl-piperidin-2-yl,  
 1-carbamoylethyl-pyrrolidin-2-yl, 2-carbamoylethyl-pyrrolidin-1-yl,  
 1-carbamoylethyl-piperidin-2-yl, 1-(pyrrolidine-2-ylcarbonyl) pyrrolidin-2-yl,  
 2-(pyrrolidine-2-ylcarbonyl) pyrrolidin-1-yl, 1-(pyrrolidine-2-ylcarbonyl)-piperidin-2-yl,  
 1-(pyrimidinyl-2-yl) pyrrolidin-2-yl, 2-(pyrimidinyl-2-yl) pyrrolidin-1-yl, 1-(pyrimidinyl-2-yl)  
 piperidin-2-yl, 1-(pyrazinyl-2-yl) pyrrolidin-2-yl, 2-(pyrazinyl-2-yl) pyrrolidin-1-yl,  
 1-(pyrazinyl-2-yl) piperidin-2-yl, 1-(pyridyl-2-yl) pyrrolidin-2-yl, 2-(pyridyl-2-yl) pyrrolidin-1-yl,  
 1-(pyridyl-2-yl) piperidin-2-yl, 1-(pyridyl-3-yl) pyrrolidin-2-yl, 2-(pyridyl-3-yl) pyrrolidin-1-yl,  
 1-(pyridyl-3-yl) piperidin-2-yl, 1-trifluoromethyl carbonyl-pyrrolidin-2-yl, 2-trifluoromethyl  
 carbonyl-pyrrolidin-1-yl, 1-trifluoromethyl carbonyl-piperidin-2-yl, 1-(2-hydroxyacetyl)  
 pyrrolidin-2-yl, 2-(2-hydroxyacetyl) pyrrolidin-1-yl, 1-(2-hydroxyacetyl) piperidin-2-yl,

1-(2-methylamino acetyl) pyrrolidin-2-yl, 2-(2-methylamino acetyl) pyrrolidin-1-yl, 1-(2-methylamino acetyl) piperidin-2-yl, 1-(2-dimethylamino acetyl) pyrrolidin-2-yl, 2-(2-dimethylamino acetyl) pyrrolidin-1-yl, 1-(2-dimethylamino acetyl) piperidin-2-yl, 1-n-propylamino acetyl-pyrrolidin-2-yl, 2-n-propylamino acetyl-pyrrolidin-1-yl, 1-n-propylamino acetyl-piperidin-2-yl, 1-isopropyl-amino acetyl-pyrrolidin-2-yl, 2-isopropyl-amino acetyl-pyrrolidin-1-yl, 1-isopropyl-amino acetyl-piperidin-2-yl and the like may be proposed.

The A ring denotes 5-6 membered nitrogen-containing heteroaromatic ring which may contain 1-3 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring represented by formula (II) (nitrogen atom represented by N\* in the formula II is excluded)



or the group condensed the said 5-6 membered heteroaromatic ring and phenyl or pyridyl.

X denotes a carbon atom or nitrogen atom.

As the A ring when it is 5-6 membered nitrogen containing heteroaromatic ring in a further embodiment, for example, thiazolyl, imidazolyl, isothiazolyl, thiadiazolyl, triazolyl, oxazolyl, oxadiazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, pyrazolyl, pyrimidinyl and the like are proposed, and among these, thiazolyl, thidiazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, triazolyl or pyrazolyl are preferred, and pyridyl, pyrazinyl, thiazolyl, thiadiazolyl, isoxazolyl or pyrazolyl are more preferred.

As a further embodiment as the A ring when it is bicyclic in which 5-6 membered nitrogen-containing aromatic ring and phenyl or pyridyl are condensed, for example, indolyl, benzimidazolyl, benzoxazolyl, pyrido thiazolyl or benzothiazolyl are proposed.

As A ring, 5-6 membered nitrogen-containing aromatic heterocycle is preferred.

Moreover, the said A ring may contain 1 or 2 substituents represented by R<sup>3</sup> described above in said ring, and when 2 substituents are present on A ring, these may be the same or different.

As R<sup>3</sup>, for example, methyl, ethoxy, hydroxymethyl, methoxycarbonyl, methoxymethyl, aminomethyl, cyano, acetyl, fluorine, chlorine, bromine or difluoromethyl and the like may be proposed.



Thus, as the A ring (the said A ring may be 1-3 substituted with R<sup>3</sup>), in further embodiment, for example 3H-imidazol-4-yl, 1H-imidazol-2-yl, [1,2,4] triazol-3-yl, [1,2,3] triazol-4-yl, pyrazol-3-yl, pyrazol-1-yl, pyridin-2-yl, pyrazin-2-yl, oxazol-2-yl, oxazol-4-yl, [1,2,4] thiadiazol-5-yl, [1,2,4] thiadiazol-3-yl, thiazol-2-yl, thiazol-4-yl, [1,2,5] thiadiazol-3-yl, pyrrole-2-yl, iso thiazol-3-yl, isoxazol-3-yl, 4-methyl-thiazol-2-yl, 4-hydroxymethyl-thiazol-2-yl, 4-methoxycarbonyl-thiazol-2-yl, 4-methoxymethyl-thiazol-2-yl, 4-aminomethyl-thiazol-2-yl, 4-cyano-thiazol-2-yl, 4-cyano-thiazol-2-yl, 4-fluoro-thiazol-2-yl, imidazol-2-yl, 4-methyl-imidazol-2-yl, 4-methoxycarbonyl-imidazol-2-yl, isothiazol-3-yl, 4-hydroxymethyl-isothiazol-3-yl, [1,3,4] thiadiazol-2-yl, 5-acetyl-[1,3,4] thiadiazol-2-yl, [1,2,4] triazol-2-yl, 5-hydroxymethyl-[1,2,4] triazol-3-yl, 4-methyl-pyridin-2-yl, 4-methoxymethyl-imidazol-2-yl, 4-acetyl-imidazol-2-yl, 5-hydroxymethyl-imidazol-2-yl, 5-methyl-[1,3,4] thiadiazol-2-yl, 5-fluoro-[1,3,4] thiadiazol-2-yl, 5-methyl-[1,2,4] triazol-2-yl, 5-acetyl-[1,2,4] triazol-3-yl, 4-methoxymethyl-isoxazol-2-yl, 5-methyl-isoxazol-3-yl, 5-hydroxymethyl-isoxazol-3-yl, 1-oxy-pyrazin-2-yl, 1-oxy-pyridin-2-yl, 5-methoxymethyl-isoxazol-3-yl, 5-methyl carbonyl-isoxazol-3-yl, 5-chloro-isoxazol-3-yl, 5-aminomethyl-isoxazol-3-yl, 4 methyl-1H-pyrazol-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridazin-3-yl, 6-methyl-pyridazin-3-yl, 2-methyl-thiazol-4-yl, thiazolo [5,4-b] pyridin-2-yl, 3-methyl-[1,2,4] thiadiazolyl-5-yl, 1-methyl-1H-pyrazol-3-yl and the like may be proposed.

R<sup>2</sup> denotes hydroxy, formyl, -CH<sub>3</sub>-F<sub>a</sub>, -OCH<sub>3</sub>-F<sub>a</sub>, amino, CN, halogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>1-4</sub>OH.

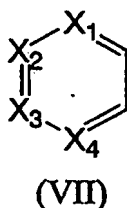
As said R<sup>2</sup>, hydroxy, formyl, -CH<sub>3</sub>-F<sub>a</sub> (preferably trifluoromethyl), -OCH<sub>3</sub>-F<sub>a</sub>, halogen, C<sub>1-6</sub> alkyl, amino, CN, -(CH<sub>2</sub>)<sub>1-4</sub>OH are preferred, hydroxy, formyl, -CH<sub>3</sub>-F<sub>a</sub> (preferably trifluoromethyl), -OCH<sub>3</sub>-F<sub>a</sub>, (preferably trifluoromethoxy), amino, halogen, -C<sub>1-6</sub> alkyl, CN or -(CH<sub>2</sub>)<sub>1-4</sub>OH are more preferred and moreover hydroxy, formyl, amino, halogen (preferably fluoro and chloro), -C<sub>1-6</sub> alkyl or -(CH<sub>2</sub>)<sub>1-4</sub>OH are still more preferably.

The q denotes an integer of 0-2.

When q is 2, R<sup>2</sup> may be the same or different.

Provided that, among the compounds represented by formula (I-0), the compounds wherein one of the X<sub>5</sub> is oxygen atom or sulfur atom and the other X<sub>5</sub> is single bond, or both X<sub>5</sub> are single bonds and R<sup>1</sup> is aryl or monocyclic or bicyclic 4-10 membered ring containing 1-4 heteroatoms in the ring which are selected from nitrogen atom, sulfur atom and oxygen atom, (as for the aforesaid R<sup>1</sup>, it may be substituted by respectively independently 1-3 of R<sup>1</sup>, moreover, when it is aliphatic heterocyclic ring, the aforesaid heterocyclic ring may have 1 or 2 double bonds) are excluded from the compounds of the invention.

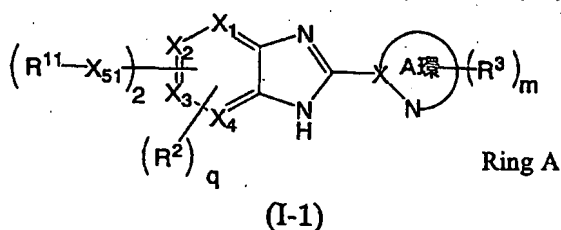
Next, the group represented by formula (VII) which is a partial structure in the said formula (I) will be explained.



$X_1$ - $X_4$  in the aforesaid formula (VII) are carbon atoms or nitrogen atoms, and at least 2 among  $X_1$ - $X_4$  denote carbon atoms.

It is more preferred that all of  $X_1$ - $X_4$  in the aforesaid formula (VII) are carbon atoms.

Moreover, as preferred form of compounds in accordance with this invention, the case wherein the compound represented by formula (I-0) is represented by formula (I-1)



[wherein,  $R^{11}$  denotes a phenyl which may be substituted with 1-3  $R^4$ , or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ), and also  $X_{51}$  denotes  $-O-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ , and the other symbols are the same as above] may be proposed.

The "phenyl which may be substituted with 1-3  $R^4$ " denoted by  $R^{11}$  denotes the aforesaid phenyl which may be substituted with 1-3  $R^4$ .

The "5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring" denoted by  $R^{11}$  denotes a group having at least one nitrogen atom in the ring as heterocycle structural atom among the aforesaid 5 or 6 membered monocycle heteroaromatic ring of  $R^1$ , and for example pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and the like may be proposed.

$X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  in formula (I-1) denote the same group of the aforesaid formula (I-0), and preferably all  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  are carbon atoms.

$R^4$  in formula (I-1) denotes the same group as  $R^4$  in the said formula (I-0).

$X_{51}$  denotes -O-, -S-, -S(O)- or -SO(O)<sub>2</sub>-, and among these, -O- or -S- is preferred, and -O- is more preferred.

Formula (I-1) has 2 groups represented by  $-X_{51}-R^{11}$ , and these may be the same or different.

As  $R^{11}-X_{51}-$  in formula (I-1) ( $R^{11}$  may be substituted 1-3 with  $R^4$ ), for example phenyl sulphonyl, phenoxy, benzyloxy, 2-cyano phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-methylcarbamoyl phenoxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 2-(pyrrolidine-1-carbonyl)-phenoxy, 3-(pyrrolidine-1-carbonyl)-phenoxy, 4-(pyrrolidine-1-carbonyl)-phenoxy, 2-methoxy-phenoxy, 3-methoxyphenoxy, 4-methoxyphenoxy, 2-isopropyl phenoxy, 3-isopropyl phenoxy, 4-isopropyl phenoxy, 2-methylphenoxy, 3-methylphenoxy, 4-methylphenoxy, 2-ethyl phenoxy, 3-ethyl phenoxy, 4-ethyl phenoxy, 2-acetyl phenoxy, 3-acetyl phenoxy, 4-acetyl phenoxy, 2-methanesulphonyl-phenoxy, 3-methanesulphonyl phenoxy, 4-methanesulphonyl phenoxy, 2-methoxycarbonyl phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-ethoxycarbonyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-hydroxyphenoxy, 3-hydroxyphenoxy, 4-hydroxyphenoxy, 2-hydroxymethyl phenoxy, 3-hydroxymethyl phenoxy, 4-hydroxymethyl phenoxy, 2-hydroxyethyl phenoxy, 3-hydroxyethyl phenoxy, 4-hydroxyethyl phenoxy, 2-formyl phenoxy, 3-formyl phenoxy, 4-formyl phenoxy, 2-(1-hydroxyethyl) phenoxy, 3-(1-hydroxyethyl) phenoxy, 4-(1-hydroxyethyl) phenoxy, 2,5-difluoro phenoxy, 2,4-difluoro phenoxy, 2,3-difluoro phenoxy, 2,6-difluoro phenoxy, 2-fluoro phenoxy, 3-fluoro phenoxy, 4-fluoro phenoxy, 2-fluoro-6-carbamoyl phenoxy, 2-difluoromethoxyphenoxy, 3-difluoromethoxyphenoxy, 4-difluoromethoxyphenoxy, 2-trifluoromethoxyphenoxy, 3-trifluoromethoxyphenoxy, 4-trifluoromethoxyphenoxy, 2-cyano-6-fluoro phenoxy, 2-(1H-tetrazol-5-yl) phenoxy, 3-(1H-tetrazol-5-yl) phenoxy, 4-(1H-tetrazol-5-yl) phenoxy, 2-(oxadiazol-3-yl) phenoxy, 3-(oxadiazol-3-yl) phenoxy, 4-(oxadiazol-3-yl) phenoxy, 2-(5-methyl oxadiazol-3-yl) phenoxy, 3-(5-methyl oxadiazol-3-yl) phenoxy, 4-(5-methyl oxadiazol-3-yl) phenoxy, 2-methoxyphenyl sulphonyl, 3-methoxyphenyl sulphonyl, 4-methoxyphenyl sulphonyl, 2-methoxyphenylmethyl sulphonyl, 3-methoxyphenylmethyl sulphonyl, 4-methoxyphenylmethyl sulphonyl,

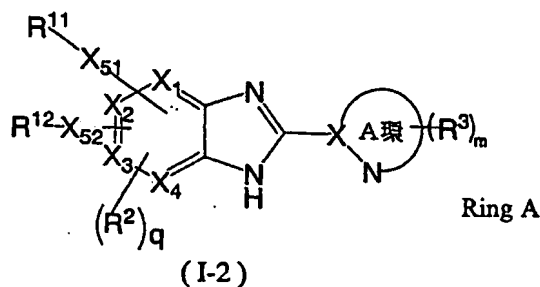
2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-(N-hydroxy amidino) phenoxy, 3-(N-hydroxy amidino) phenoxy, 4-(N-hydroxy amidino) phenoxy, pyridin-2-yl sulphanyl, pyridin-3-yl sulphanyl, pyridin-4-yl sulphanyl, pyridin-2-yloxy, pyridin-3-yloxy, pyridine-4-yloxy, 2-methoxypyridin-3-yloxy, 2-methoxypyridine-4-yloxy, 6-methoxypyridin-3-yloxy, 6-methoxypyridin-2-yloxy, 3-methoxypyridin-2-yloxy, 4-methoxypyridin-2-yloxy, 5-methoxypyridin-2-yloxy, 2-difluoromethoxypyridin-3-yloxy, 6-methylpyridin-2-yl sulphanyl, 5-methylpyridin-2-yl sulphanyl, 4-methylpyridin-2-yl sulphanyl, 3-methylpyridin-2-yl sulphanyl, 4-cyano-pyridin-3-yloxy, 4-dimethylcarbamoyl-pyridin-3-yloxy, 4-methanesulphonyl-pyridin-3-yloxy, 2-cyano-pyridin-3-yloxy, 2-dimethylcarbamoyl-pyridin-3-yloxy, 2-methanesulphonyl-pyridin-3-yloxy, 2-methylpyridin-3-yl sulphanyl, 4-methylpyridin-3-yl sulphanyl, 5-methylpyridin-3-yl sulphanyl, 6-methylpyridin-3-yl sulphanyl, 2-methylpyridin-4-yl sulphanyl, 3-methylpyridin-4-yl sulphanyl, 4-methylpyridin-3-yl sulfonyl, 5-methylpyridin-3-yl sulfonyl, 6-methylpyridin-3-yl sulfonyl, 2-methylpyridin-3-yl sulfonyl, 3-methylpyridin-2-yl sulfonyl, 4-methylpyridin-2-yl sulfonyl, 5-methylpyridin-2-yl sulfonyl, 6-methylpyridin-2-yl sulfonyl, 2-oxo-1,2-dihydropyridin-3-yloxy, 1-methyl-2-oxo-1,2-dihydropyridin-3-yloxy, 1-ethyl-2-oxo-1,2-dihydropyridin-3-yloxy, 1H-imidazol-2-yl sulphanyl, 1-methyl-1H-imidazol-2-yl sulphanyl, 4H-[1,2,4] triazol-3-yl sulphanyl or 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl and the like may be proposed.

As preferred form of the compounds in accordance with this invention, the case wherein both  $R^{11}$  in the said formula (I-1) are phenyls which may be substituted by 1-3 of the aforesaid  $R^4$  may be proposed.

Moreover, as preferred form of compound in accordance with this invention, the case wherein both  $R^{11}$  in the said formula (I-1) are 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ) may be proposed.

Moreover, as preferred form of compound in accordance with this invention, the case wherein one of  $R^{11}$  in the said formula (I-1) is a phenyl which may be substituted by 1-3 of the aforesaid  $R^4$  and the other  $R^{11}$  is 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and the oxygen atom in the ring (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ) may be proposed.

Moreover, as preferred form of compound in accordance with this invention, the case wherein the compound represented by formula (I-0) is formula (I-2)



[wherein,  $R^{12}$  denotes 5-7 membered nitrogen-containing heterocycle containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said  $R^{12}$  may be substituted with the aforesaid  $R^4$  of 1-3, and moreover when said  $R^{12}$  is aliphatic hetero ring, it may contain 1 or 2 double bonds in the ring), and  $X_{52}$  is -O-, -S-, -S(O), -S(O)<sub>2</sub>- or single bond, and the other symbols are the same as above) may be proposed.

The "4-7 membered nitrogen-containing heterocycle containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, may containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring" denoted by  $R^{12}$  denotes 4-7 membered monocyclic heterocycle of the said R1 and also a group having at least one nitrogen atom in heterocycle, and for example azetidiny, pyrrolidinyl, piperidinyl, azepanyl, piperazinyl, morpholino, thiomorpholino, homopiperazinyl, imidazolidinyl, pyrazolidinyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl and the like may be proposed.

$R^{12}$  may have 1-3 of the aforesaid  $R^4$  as substituents.

When  $R^{12}$  contains 2 or 3  $R^4$  as substituents, these may be the same or different.

As substituent of  $R^{12}$ , among the aforesaid  $R^4$ , -C(O)-C<sub>1-6</sub> alkyl of (the said C<sub>1-6</sub> alkyl may be substituted with halogen, hydroxy, -N(R<sup>51</sup>)R<sup>52</sup>-, -O-C<sub>1-6</sub> alkyl or phenyl), -C(O)-phenyl, -C(O)-C<sub>3-7</sub> cycloalkyl, -C(O)-O-C<sub>1-6</sub> alkyl, -C(O)-N(R<sup>51</sup>)R<sup>52</sup>-, -C<sub>1-6</sub> alkyl, heteroaromatic ring, -S(O)<sub>2</sub>-N(R<sup>51</sup>)R<sup>52</sup>-, -S(O)<sub>2</sub>-C<sub>1-6</sub> alkyl are preferred.

As substituent of  $R^{12}$ , for example, acetyl, ethyl carbonyl, propyl carbonyl, isopropyl carbonyl, hydroxyethyl carbonyl, hydroxymethyl carbonyl, methoxymethyl carbonyl, ethoxymethyl carbonyl, methyl, ethyl, phenyl carbonyl, phenethyl carbonyl, benzyl carbonyl, dimethylaminomethyl carbonyl, methylaminomethyl carbonyl, cyclohexyl carbonyl, cyclopentyl carbonyl, 1-methyl-3-oxo butyl carbonyl, methanesulphonyl, ethanesulphonyl, isopropyl sulfonyl, carbamoyl, carbamoylmethyl, carbamoylethyl, pyrrolidine-2-carbonyl, pyrimidinyl, pyrazinyl,

pyridyl, trifluoromethyl carbonyl, 2-hydroxyacetyl, 2-methylamino acetyl, 2-dimethylamino acetyl, 2-ethylamino acetyl, n-propylamino acetyl, isopropyl amino acetyl, oxo, methyl, ethyl, isopropyl and the like may be proposed.

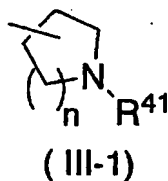
$X_{51}$  in formula (1-2) among the aforesaid  $X_{51}$ , -O- or -O- is preferred, and -O- is more preferred.

$X_{52}$  in formula (1-2) denotes -O-, -S-, -S(O)-, -S(O)<sub>2</sub>- or single bond.

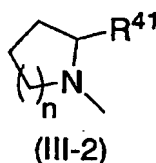
When  $R^{12}$  is 4-7 membered saturated nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said nitrogen containing aliphatic hetero ring may be substituted with the aforesaid  $R^4$  of 1-3),  $X_{52}$  is preferred to be a single bond.

When  $R^{12}$  is 5-7 membered nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, and moreover containing 1 or 2 double bonds in the ring (the said 5-7 membered heterocycle may be substituted with 1-3 of the aforesaid  $R^4$ ), -O-, -S-, -S(O)- or S(O)<sub>2</sub>- is preferred as  $X_{52}$ , and -O- is more preferable.

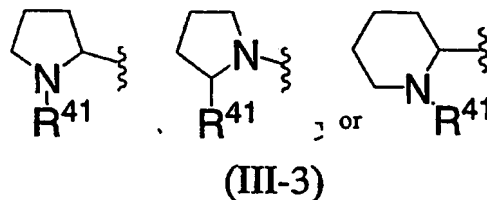
As "4-7 membered saturated nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom" denoted by  $R^{12}$ , for example azetidiny, pyrrolidiny, piperidine, piperidiny, homo piperidiny, azepany, piperaziny, morpholino, thiomorpholino, homopiperaziny, imidazolidiny, pyrazolidiny and the like are proposed, and among these, azetidiny, pyrrolidiny or piperidiny are preferred, and pyrrolidiny, piperidiny, homo piperidiny are preferred, and the group represented by formula (III-1)



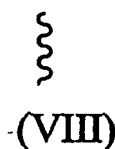
or (III-2)



[wherein, n denotes an integer of 1-3 and  $R^{41}$  is the same as aforesaid  $R^4$ ] is more preferably, and the group by formula (III-3)



[wherein,  $R^4$  denotes the same groups as in the aforesaid definition, and formula (VIII)



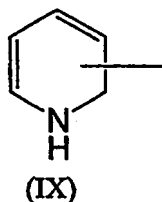
denotes binding site of  $X_{53}$ ] is still more preferred.

As "4-7 membered saturated nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said nitrogen containing aliphatic hetero ring may be substituted with 1-3 of the aforesaid  $R^4$ )" denoted by  $R^{12}$ , for example 1-acetyl pyrrolidin-2-yl, 2-acetyl pyrrolidin-1-yl, 1-acetyl-3-fluoro pyrrolidin-2-yl, 1-acetyl-5-methylpyrrolidin-2-yl, 1-acetyl piperidin-2-yl, 1-ethyl carbonyl-pyrrolidin-2-yl, 2-ethyl carbonyl pyrrolidin-1-yl, 1-ethyl carbonyl-piperidin-2-yl, 1-n-propyl carbonyl-pyrrolidin-2-yl, 2-n-propyl carbonyl-pyrrolidin-2-yl, 1-n-propyl carbonyl-piperidin-2-yl, 1-isopropyl-pyrrolidin-2-yl, 2-isopropyl-pyrrolidin-1-yl, 1-isopropyl-piperidin-2-yl, 1-hydroxyethyl carbonyl-pyrrolidin-2-yl, 2-hydroxyethyl carbonyl-pyrrolidin-1-yl, 1-hydroxyethyl carbonyl-piperidin-2-yl, 1-hydroxymethyl carbonyl-pyrrolidin-2-yl, 2-hydroxymethyl carbonyl-pyrrolidin-1-yl, 1-hydroxymethyl carbonyl-piperidin-2-yl, 1-methoxymethyl carbonyl-pyrrolidin-2-yl, 2-methoxymethyl carbonyl-pyrrolidin-1-yl, 1-methoxymethyl carbonyl-piperidin-2-yl, 1-ethoxymethyl carbonyl-pyrrolidin-2-yl, 2-ethoxymethyl carbonyl-pyrrolidin-1-yl, 1-ethoxymethyl carbonyl-piperidin-2-yl, 1-methylpyrrolidin-2-yl, 2-methylpyrrolidin-1-yl, 1-methylpiperidin-2-yl, 1-ethylpyrrolidin-2-yl, 2-ethylpyrrolidin-1-yl, 1-ethylpiperidin-2-yl, 1-phenyl carbonyl-pyrrolidin-2-yl, 2-phenyl carbonyl-pyrrolidin-1-yl, 1-phenyl carbonyl-piperidin-2-yl, 1-phenethyl carbonyl-pyrrolidin-2-yl, 2-phenethyl carbonyl-pyrrolidin-1-yl, 1-phenethyl carbonyl-piperidin-2-yl, 1-benzyl carbonyl-pyrrolidin-2-yl, 2-benzyl carbonyl-pyrrolidin-1-yl, 1-benzyl carbonyl-piperidin-2-yl, 1-dimethylaminomethyl carbonyl-pyrrolidin-2-yl, 2-dimethylaminomethyl carbonyl-pyrrolidin-1-yl, 1-dimethylaminomethyl carbonyl-piperidin-2-yl, 1-methylaminomethyl carbonyl-pyrrolidin-2-yl, 2-methylaminomethyl

carbonyl-pyrrolidin-1-yl, 1-methylaminomethyl carbonyl-piperidin-2-yl, 1-cyclohexyl  
 carbonyl-pyrrolidin-2-yl, 2-cyclohexyl carbonyl-pyrrolidin-1-yl, 1-cyclohexyl  
 carbonyl-piperidin-2-yl, 1-cyclopentyl carbonyl-pyrrolidin-2-yl, 2-cyclopentyl  
 carbonyl-pyrrolidin-1-yl, 1-cyclopentyl carbonyl-piperidin-2-yl, 1-(1-methyl-3-oxobutyl  
 carbonyl)-pyrrolidin-2-yl, 2-(1-methyl-3-oxobutyl carbonyl)-pyrrolidin-1-yl,  
 1-(1-methyl-3-oxobutyl carbonyl)-piperidin-2-yl, 1-methanesulphonyl-pyrrolidin-2-yl,  
 2-methanesulphonyl-pyrrolidin-1-yl, 1-methanesulphonyl-piperidin-2-yl,  
 1-ethanesulphonyl-pyrrolidin-2-yl, 2-ethanesulphonyl-pyrrolidin-1-yl,  
 1-ethanesulphonyl-piperidin-2-yl, 1-isopropyl sulfonyl-pyrrolidin-2-yl, 2-isopropyl  
 sulfonyl-pyrrolidin-1-yl, 1-isopropyl sulfonyl-piperidin-2-yl, 1-carbamoyl-pyrrolidin-2-yl,  
 2-carbamoyl-pyrrolidin-1-yl, 1-carbamoyl-piperidin-2-yl, 1-carbamoylmethyl-pyrrolidin-2-yl,  
 2-carbamoylmethyl-pyrrolidin-1-yl, 1-carbamoylmethyl-piperidin-2-yl,  
 1-carbamoylethyl-pyrrolidin-2-yl, 2-carbamoylethyl-pyrrolidin-1-yl,  
 1-carbamoylethyl-piperidin-2-yl, 1-(pyrrolidine-2-ylcarbonyl) pyrrolidin-2-yl,  
 2-(pyrrolidine-2-ylcarbonyl) pyrrolidin-1-yl, 1-(pyrrolidine-2-ylcarbonyl)-piperidin-2-yl,  
 1-(pyrimidinyl-2-yl) pyrrolidin-2-yl, 2-(pyrimidinyl-2-yl) pyrrolidin-1-yl, 1-(pyrimidinyl-2-yl)  
 piperidin-2-yl, 1-(pyrazinyl-2-yl) pyrrolidin-2-yl, 2-(pyrazinyl-2-yl) pyrrolidin-1-yl,  
 1-(pyrazinyl-2-yl) piperidin-2-yl, 1-(pyridyl-2-yl) pyrrolidin-2-yl, 2-(pyridyl-2-yl) pyrrolidin-1-yl,  
 1-(pyridyl-2-yl) piperidin-2-yl, 1-(pyridyl-3-yl) pyrrolidin-2-yl, 2-(pyridyl-3-yl) pyrrolidin-1-yl,  
 1-(pyridyl-3-yl) piperidin-2-yl, 1-trifluoromethyl carbonyl-pyrrolidin-2-yl, 2-trifluoromethyl  
 carbonyl-pyrrolidin-1-yl, 1-trifluoromethyl carbonyl-piperidin-2-yl, 1-(2-hydroxyacetyl)  
 pyrrolidin-2-yl, 2-(2-hydroxyacetyl) pyrrolidin-1-yl, 1-(2-hydroxyacetyl) piperidin-2-yl,  
 1-(2-methylamino acetyl) pyrrolidin-2-yl, 2-(2-methylamino acetyl) pyrrolidin-1-yl,  
 1-(2-methylamino acetyl) piperidin-2-yl, 1-(2-dimethylamino acetyl) pyrrolidin-2-yl,  
 2-(2-dimethylamino acetyl) pyrrolidin-1-yl, 1-(2-dimethylamino acetyl) piperidin-2-yl,  
 1-n-propylamino acetyl-pyrrolidin-2-yl, 2-n-propylamino acetyl-pyrrolidin-1-yl, 1-n-propylamino  
 acetyl-piperidin-2-yl, 1-isopropyl-aminoacetyl-pyrrolidin-2-yl, 2-isopropylamino  
 acetyl-pyrrolidin-1-yl, 1-isopropylamino acetyl-piperidin-2-yl and the like may be proposed.

As "5-7 membered nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, and moreover containing 1 or 2 double bonds in the ring" denoted by R<sup>12</sup>, as embodiments, for example group represented by formula (IX)



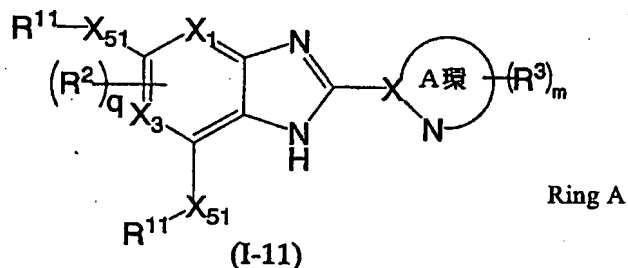


and the like may be proposed.

As "5-7 membered nitrogen-containing aliphatic hetero ring containing at least one nitrogen atom as atom constituted heterocycle and as other heteroatom, optionally containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, and moreover containing 1 or 2 double bonds in the ring (the said nitrogen-containing aliphatic hetero ring may be substituted with the aforesaid R<sup>4</sup> of 1-3)" denoted by R<sup>12</sup>, as embodiments, for example 1-methyl-2-oxo-1,2-dihydropyridyl, 2-oxo-1,2-dihydropyridyl, 1-ethyl-2-oxo-1,2-dihydropyridyl, 1-isopropyl-2-oxo-1,2-dihydropyridyl, 1-propyl-2-oxo-1,2-dihydropyridyl and the like may be proposed.

Moreover, as R<sup>11</sup>-X<sub>51</sub> in formula (1-2) (R<sup>11</sup> may be substituted 1-3 with the aforesaid R<sup>4</sup>), the same groups as in the said formula (I-1) is proposed. Among these, for example, 5-bromopyridin-2-yloxy, 6-methanesulphonyl-pyridin-3-yloxy, 2-chloropyridin-3-yloxy, 4-hydroxy methoxymethyl-phenoxy, 4-methanesulphonyl phenoxy, 6-ethanesulphonyl-pyridin-3-yloxy, 6-cyanopyridin-3-yloxy, 6-acetylamino-pyridin-3-yloxy, 4-methoxymethyl-phenoxy, 4-(2-oxo-2H-pyridine-1-yl) phenoxy, 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yloxy, 2'-fluorobiphenyl-4-yloxy, 6-([1,2,4]-oxadiazol-3-yl) pyridin-3-yloxy, 6-(2-methyl-2H-tetrazol-5-yl)-pyridin-3-yloxy, 4-(2-methyl-2H-tetrazol-5-yl) phenoxy, 6-methoxymethyl-pyridin-3-yloxy, 2-oxo-2H-[1,3'] bipyridine-6'-yloxy, 5-(2-oxo-oxazolidinone-3-yl) pyridin-2-yloxy, 6-methylpyridin-3-yloxy, 6-pyrazin-2-yl pyridin-3-yloxy, 4-acetyl phenoxy and the like are preferred.

As preferred embodiment of the compounds in accordance with this invention, for example, the case that compound represented by the aforesaid formula (I-1) is shown by formula (I-11)



(each symbol is the same as above) may be proposed.

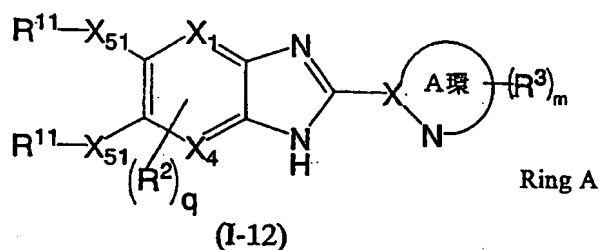
As  $R^{11}$  in formula (I-11) (the said  $R^{11}$  may be substituted with 1-3 of the aforesaid  $R^4$ ), the same groups as in  $R^{11}$  in the said formula (I-1) may be proposed.

As  $X_{51}$  in formula (I-11), -O- or -S- is preferred, and -O- is more preferred.

$X_1$  and  $X_3$  in formula (I-11) each independently denote carbon atom or nitrogen atom, but the case that both  $X_1$  and  $X_3$  are carbon atoms is preferred.

As  $R^{11}-X_{51}-$  in formula (I-11) (said  $R^{11}$  may be substituted by the aforesaid  $R^4$  of 1-3), as embodiments, for example, methanesulphonyl phenoxy, 3-methanesulphonyl phenoxy, 2-methoxyphenoxy, 3-methoxyphenoxy, 2-acetyl phenoxy, 3-acetyl phenoxy, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, phenoxy, 2-cyano-6-fluoro phenoxy, 2-methylphenoxy, 3-methylphenoxy, 2-fluoro phenoxy, 3-fluoro phenoxy, 2,3-difluoro phenoxy, 2,4-difluoro phenoxy, 2,5-difluoro phenoxy, 2,6-difluoro phenoxy, pyridin-2-yloxy, pyridin-3-yloxy, 2-methoxypyridin-3-yloxy, 2-difluoromethoxypyridin-3-yloxy and the like are proposed, and among these, 2-methanesulphonyl phenoxy, 2-methoxyphenoxy, 2-acetyl phenoxy, 2-carbamoyl phenoxy, phenoxy, 2-cyano-6-fluoro phenoxy, 2-methylphenoxy, 2-fluoro phenoxy, 2,3-difluoro phenoxy, 2,6-difluoro phenoxy, pyridin-3-yloxy, 2-methoxypyridin-3-yloxy, 2-difluoromethoxypyridin-3-yloxy and the like are preferred.

Moreover, for example, as preferred form of compound in accordance with this invention, the case that compound represented by the aforesaid formula (I-1) is shown by formula (I-12)



(each symbol is the same as above) may be proposed.

$R^{11}$  in formula (I-12) (the said  $R^{11}$  may be substituted with the aforesaid  $R^4$  of 1-3), the same groups as in  $R^{11}$  in the said formula (I-1) may be proposed.

As  $X_{51}$  in formula (I-12), -O- or -S- is preferred, and -O- is more preferred.

$X_1$  and  $X_3$  in formula (I-12) each independently denote carbon atom or nitrogen atom, but the case that both  $X_1$  and  $X_3$  are carbon atoms is preferred.

As  $R^{11}-X_{51}$ - in formula (I-12), in an embodiment for example, 2-carbamoyl phenoxy, 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-cyano phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 2-methoxy phenoxy, 3-methoxy phenoxy, 4-methoxy phenoxy, 2-methansulfonyl phenoxy, 3-methansulfonyl phenoxy, 4-methansulfonyl phenoxy, 2-(pyrrolidin-1-carbonyl)-phenoxy, 3-(pyrrolidin-1-carbonyl)-phenoxy, 4-(pyrrolidin-1-carbonyl)-phenoxy, pyridin-2-yloxy, pyridine-3-yloxy, pyridine-4-yloxy, 2-methylcarbamoyl phenoxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 2-(oxazol-3-yl) phenoxy, 2-methoxycarbonyl phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-acetylphenoxy, 3-acetylphenoxy, 4-acetylphenoxy, 2-ethoxycarbonyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-N-hydroxy amidino-phenoxy, 3-N-hydroxy amidino-phenoxy, 4-N-hydroxy amidino-phenoxy, 2-hydroxymethyl-phenoxy, 3-hydroxymethyl-phenoxy, 4-hydroxymethyl-phenoxy, 2-(2H-tetrazol-5-yl) phenoxy, 3-(2H-tetrazol-5-yl) phenoxy, 4-(2H-tetrazol-5-yl) phenoxy, 2-cyano-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 2-carbamoyl-pyridin-3-yl, 2-difluoromethoxy-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yl, 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-formyl phenoxy, 3-formyl phenoxy, 4-formyl phenoxy and the like may be proposed.

Among these, for example, one of  $R^{11}-X_{51}$ - is preferred to be 2-carbamoyl phenoxy, 4-carbamoyl phenoxy, 2-cyano phenoxy, 4-cyano phenoxy, 2-methoxy phenoxy, 4-methoxy phenoxy, 2-methansulfonyl phenoxy, 4-methansulfonyl phenoxy, pyridin-2-yloxy, pyridin-3-yloxy, pyridin-4-yloxy, 2-cyano-pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 2-carbamoyl-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yloxy, 5-cyano-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 5-carbamoyl-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yloxy, 2-methylcarbamoyl phenoxyoxy, 4-methylcarbamoyl phenoxyoxy, 2-dimethylcarbamoyl phenoxyoxy, 4-dimethylcarbamoyl phenoxyoxy, 2-(oxadiazol-3-yl) phenoxy, 2-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 2-acetyl phenoxy, 4-acetyl phenoxy, 2-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 2-N-hydroxyamidino-phenoxy, 4-N-hydroxyamidino-phenoxy, 2-hydroxymethyl-phenoxy, 4-hydroxymethyl-phenoxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-(2H-tetrazol-5-yl) phenoxy, 4-(2H-tetrazol-5-yl) phenoxy, 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-formyl phenoxy, 4-formyl phenoxy and the like, and to be 2-carbamoyl phenoxy, 2-cyano phenoxy, 2-methoxyphenoxy, 2-methanesulphonyl phenoxy, pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-methylcarbamoyl phenoxy, 2-dimethylcarbamoyl phenoxy, 2-(oxadiazol-3-yl) phenoxy, 2-methoxycarbonyl phenoxy,

2-acetyl phenoxy, 2-ethoxycarbonyl phenoxy, 2-N-hydroxy amidino-phenoxy, 2-cyano-pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-carbamoyl-pyridin-3-yloxy, 2-hydroxymethyl-phenoxy, 2-(2H-tetrazol-5-yl) phenoxy, 2-difluoromethoxy-pyridin-3-yloxy, 2-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 2-formyl phenoxy and the like is more preferred.

For example, the other  $R^{11}$ -X<sub>51</sub>- is preferred to be 3-carbamoyl phenoxy, 4-carbamoyl phenoxy, 3-cyano phenoxy, 4-cyano phenoxy, 3-methoxyphenoxy, 4-methoxyphenoxy, 3-(pyrrolidine-1-carbonyl)-phenoxy, 4-(pyrrolidine-1-carbonyl)-phenoxy, 3-methanesulphonyl phenoxy, 4-methanesulphonyl phenoxy, pyridin-2-yloxy, pyridin-3-yloxy, pyridine-4-yloxy, 2-difluoromethoxy-pyridin-3-yloxy, 3-methylcarbamoyl phenoxy, 4-methylcarbamoyl phenoxy, 5-cyano-pyridin-3-yloxy, 4-cyano-pyridin-3-yloxy, 5-carbamoyl-pyridin-3-yloxy, 4-carbamoyl-pyridin-3-yloxy, 3-dimethylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 4-(oxadiazol-3-yl) phenoxy, 3-methoxycarbonyl phenoxy, 4-methoxycarbonyl phenoxy, 3-acetyl phenoxy, 4-acetyl phenoxy, 3-ethoxycarbonyl phenoxy, 4-ethoxycarbonyl phenoxy, 3-N-hydroxy amidino-phenoxy, 4-N-hydroxy amidino-phenoxy, 3-hydroxymethyl-phenoxy, 4-hydroxymethyl-phenoxy, 3-(2H-tetrazol-5-yl) phenoxy, 4-(2H-tetrazol-5-yl) phenoxy, 3-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 3-formyl phenoxy, 4-formyl phenoxy and the like, and to be 4-carbamoyl phenoxy, 4-cyanophenoxy, 4-methoxyphenoxy, 4-methanesulphonyl phenoxy, pyridin-3-yloxy, 4-methylcarbamoyl phenoxy, 4-dimethylcarbamoyl phenoxy, 4-(oxadiazol-3-yl) phenoxy, 4-methoxycarbonyl phenoxy, 4-acetyl phenoxy, 4-ethoxycarbonyl phenoxy, 4-N-hydroxy amidino-phenoxy, 4-hydroxymethyl-phenoxy, 4-cyano-pyridin-3-yloxy, 2-difluoromethoxy-pyridin-3-yloxy 4-carbamoyl-pyridin-3-yloxy, 4-(2H-tetrazol-5-yl) phenoxy, 4-(5-oxo-4,5-dihydro-[1,2,4] oxadiazol-3-yl) phenoxy, 4-formyl phenoxy and the like is more preferred.

Moreover, as preferred form of compound in accordance with this invention, compound in accordance with this invention is compound represented by formula (I-0) and the case wherein one of R<sup>1</sup> is phenyl which may be substituted by 1-3 R<sup>4</sup> or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3 R<sup>4</sup>) and also the other R<sup>1</sup> is 5-7 membered nitrogen-containing heterocycle having at least one nitrogen atom as heteroatom constituted heterocycle, and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, may be proposed.

As said 5-7 membered nitrogen-containing heterocycle, 5 or 6 membered nitrogen-containing

heteroaromatic ring or 5-7 membered nitrogen-containing aliphatic hetero ring may be proposed.

As 5 or 6 membered nitrogen-containing heteroaromatic ring, for example, pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and the like may be proposed.

As the 5-7 membered nitrogen-containing aliphatic heterocycle, for example, azetidiny, pyrrolidinyl, piperidino, piperidinyl, azepanyl, piperazinyl, morpholino, thiomorpholino, homopiperazinyl, imidazolidinyl, pyrazolidinyl and the like may be proposed.

The said heterocycle may be substituted with 1-3 of the aforesaid  $R^4$ , and moreover when said heterocycle is aliphatic hetero ring, it may contain 1 or 2 double bond.

Moreover, as preferred form of compound in accordance with this invention, compound in accordance with this invention is compound represented by formula (I-0) and the case wherein one of  $R^1$  is phenyl which may be substituted by 1-3  $R^4$  or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted by 1-3  $R^4$ ) and also the other  $R^1$  is 5-7 membered nitrogen-containing heteroaromatic ring having at least one nitrogen atom as heteroatom constituted heterocycle, and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, may be proposed.

As 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, the same groups as in an item mentioned above may be proposed.

Moreover, as preferred form of compound in accordance with this invention, compound in accordance with this invention is compound represented by formula (I-0) and the case wherein one of  $R^1$  is phenyl which may be substituted by 1-3  $R^4$  or 5 or 6 membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted by 1-3  $R^4$ ) and also the other  $R^1$  is 5-7 membered nitrogen-containing aliphatic hetero ring having at least one nitrogen atom as heteroatom constituted heterocycle, and as other heteroatom, optionally containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen containing aliphatic hetero ring may be substituted by 1-3  $R^4$ , and moreover may contain 1 or 2 double bond in the ring) may be proposed.

Among compound represented by formula (I-0), for example,

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole,  
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole,  
5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,6-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-cyanopyridin-3-yloxy)-6-(6-ethanesulphonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-

-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulphonyl-phenoxy)-1H-benzimidazole,  
5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2-fluoro-phenoxy)-2-(pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole,  
4-(2-fluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
4-(2,3-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

le,  
4-(2,5-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
le,  
4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
1-(2-(6-(5-bromo-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide,  
2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile,  
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylamino-ethanone,  
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
N-(5-(6-[1-acetyl-pyrrolidin-2-yl]-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide,  
1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,



N-(2-(2-[6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl]-pyrrolidin-1-yl)-2-oxo-ethyl)-acetamide,  
6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • mono trifluoroacetate,  
1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridin-2(1H)-one,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
(2-(2-(5-((2'-fluorobiphenyl-4-yl-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine),  
6-(1-acetylpyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl] pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(1-acetyl-3-fluoropyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(6'-[methoxymethylpyridin-3-yl] oxy)-2-pyridin-2-yl-1H-benzimidazole,  
2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol,  
2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide,  
5'-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one,  
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,  
6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-pyrazin-2-ylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetyl-3-fluoropyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)

oxy)-2-pyridin-2-yl-1H-benzimidazole,  
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy)  
phenyl)-1,3-oxazolidin-2-one,  
6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-5-((6-pyrazin-2-ylpyridin-3-yl)  
oxy)-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)  
oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl)  
phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzi  
midazole,  
N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)  
pyrrolidin-1-yl)-2-oxo ethanamine,  
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl)  
oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-et  
hanone,  
1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-  
2-yl)-ethanone,  
1-(1-(6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-  
yl)-ethanone, or  
1-(1-(6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrr  
olidin-2-yl)-ethanone or pharmacologically acceptable salts thereof and the like may be proposed.

The novel-2-heteroaryl substituted benzimidazole derivatives in accordance with this invention can be present as pharmacologically acceptable salts. As the aforesaid salts, acid addition salt or base addition salt may be proposed.

As for the compounds in accordance with this invention, there are cases that stereoisomers, tautomers or the like such as optical isomers, diastereoisomer, geometric isomer exist according to the type of substituents thereof. Needless to say that these isomers are all included in the compounds in accordance with this invention. Again, needles to say that arbitrary mixture of isomers thereof is included in the compounds in accordance with this invention.

Because the compounds of this invention have glucokinase activation action, the said compounds are useful as a therapeutic agent and/or preventive agent of diabetes mellitus, furthermore as a therapeutic agent and/or preventive agent of diabetic complications.

Wherein, the complications of diabetes mellitus are diseases that occur as a result of the onset of diabetes mellitus, and as the said complications of diabetes mellitus for example, diabetic nephropathy, diabetic retinopathy, diabetic neurosis, diabetic arteriosclerosis and the like are nominated.

Compounds in accordance with this invention can be applicable to both types of diabetes mellitus of insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM)

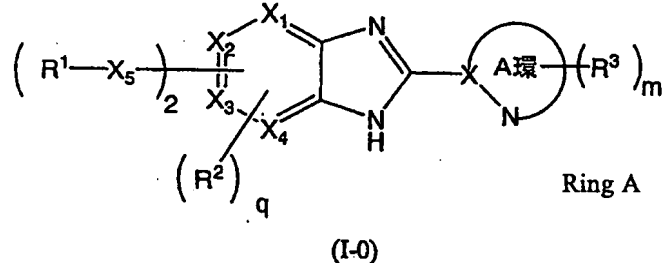
Moreover, the insulin-dependent diabetes mellitus (IDDM) is thought to occur due to predisposition of hereditary insulin secretion lowering and insulin resistance in the skeletal muscle with addition of insulin resistance caused by obesity, and is considered mainly as an adult onset.

The compounds in accordance with this invention are thought to be useful for type II diabetes mellitus that was impossible to achieve satisfactory lowering of blood glucose level with prior art diabetes mellitus drugs, in addition to type I insulin-dependent diabetes mellitus.

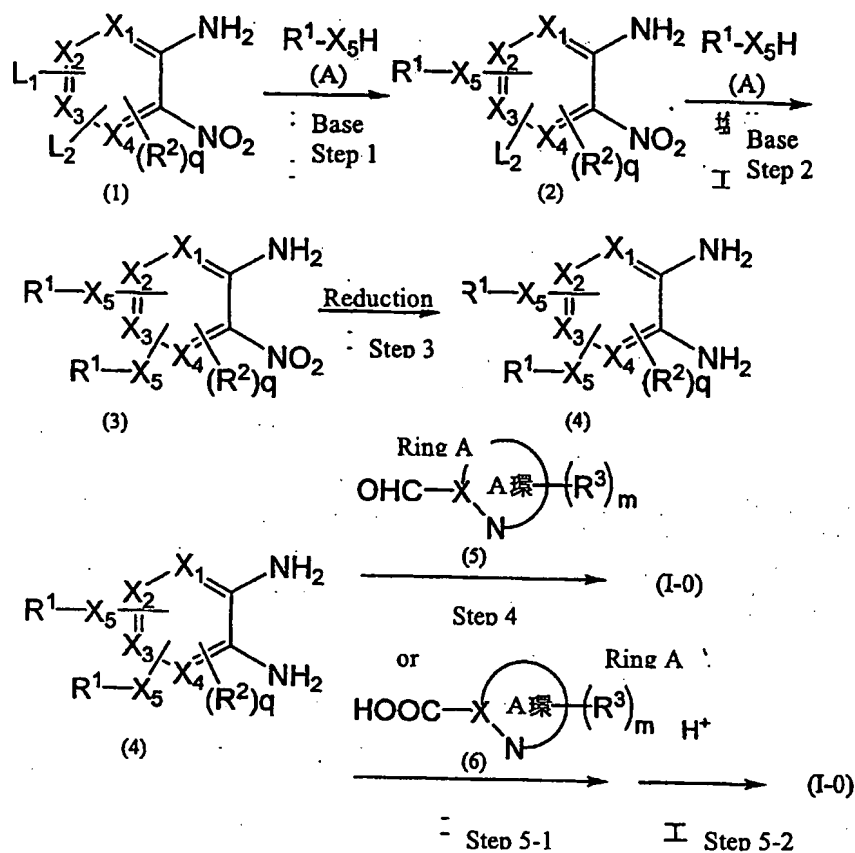
Moreover, in type II diabetes mellitus, it is remarkable that the degree of postprandial hyperglycemia is prolonged compared with healthy person, and the compound in accordance with this invention or pharmacologically acceptable salts thereof are useful for this type II diabetes mellitus.

Moreover, the compounds in accordance with this invention or pharmacologically acceptable salts thereof are useful for the therapy and/or prevention of obesity.

The compound represented by formula (I-0)



(in the formula, each symbol has the same the aforesaid definitions) in accordance with this invention can be produced, for example, using the following process.



(wherein,  $L^1$  and  $L^2$  denote leaving group such as halogen or the like, and each symbol has the same definitions as aforesaid).

(Step 1).

This step is process to produce compound (2) by reacting compound (1) with compound (A) represented by formula  $R^1-X_5H$  in the presence of base. More specifically, for example, as  $L^1$  and  $L^2$ , halogen such as fluorine, chlorine and bromine or the like may be proposed.  $L^1$  and  $L^2$  may be the same or different.

As the compound (1) used in this step, for example, 3,5-difluoro-2-nitroaniline, 3,5-dichloro-2-nitroaniline, 3,5-dibromo-2-nitroaniline, 4-bromo-5-fluoro-2-nitroaniline, 4,5-difluoro-2-nitroaniline and the like may be proposed.

Amount of compound (A) used differs depending on compound and kind of solvent, other reaction conditions used, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (1).

Amount of base used differs depending on compound which is used, kind of solvent and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used in this step, any one in which reaction of compound (1) and  $R5-X_3H$  produced compound (2) may be used, but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed. When  $R5-X_3H$  is primary or secondary amine, there does not need to be using base.

As the reaction solvent which is used, it is not restricted in particular so long as it is inert solvent which does not inhibit the reaction, as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is 250 degrees, preferably 0-150 degrees, in this step.

Usually the reaction time is between 0.1-72 hours, preferably from 30 minutes to 5 hours in this step.

Compound (2) obtained in this way can be subjected to next step without being isolated and purified, or after isolation and purification using the like of well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 2).

This step is process to produce compound (3) by reacting compound (2) obtained in the aforesaid step 1 with the same compound (A) as in the aforesaid step 1 or a different compound (A), in the presence of base.

This step can be carried out by the same process as in the aforesaid step 1, a process based on this, or combination of these and the conventional procedure.

(Step 3).

This step is process to produce compound (4) by reducing nitro group of compound (3) obtained in the aforesaid step 2.

As for reductive reaction which is used, process well-known to a person skilled in the art is used in this step.

As the reductive reaction used in this step, as embodiments, for example, catalytic reduction method using hydrogen, formic acid, ammonium formate, hydrazine hydrate and palladium, platinum, nickel catalyst; a reduction method using hydrochloric acid, ammonium chloride and iron, a reduction method using methanol and tin chloride; and the like may be proposed.

Amount of reducing agent used in the aforesaid reductive reaction differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 1-50 equivalents, preferably 2-20 equivalents with respect to 1 equivalent of compound (3).

The reaction solvent which is used is not restricted in particular, so long as there is no hindrance to the reaction, for example methanol, N,N-dimethylformamide, ethyl acetate, tetrahydrofuran and the like and mixed solvent thereof can be used.

The reaction temperature and the reaction time are not restricted in particular. However, it is reacted for about 1-20 hours, preferably 1 to 5 hours approx at the reaction temperature of about -10 to 100°C, preferably around 0-50°C.

Compound (4) obtained in this way can be subjected to next step without being isolated and purified or can be isolated and purified by using the like of well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 4).

This step is process to produce compound (1) by reacting compound (4) obtained in the aforesaid step 3 with compound (5).

In this step cyclisation reaction is carried out by process in accordance with literature (for example, Synthesis, 10 1380-1390 (2000) or the like), or a process based on this, or a combination of these and a conventional procedure.

As compound (5) used, for example, pyridine carboxaldehyde, pyrazine carboxaldehyde, 1H-pyrazole-3-carboxaldehyde and the like may be proposed.

Compound (5) is usually used at 0.1-100 equivalents, preferably 0.1-3 equivalents.

Reaction solvent which is used in this step is not restricted in particular provided it does not hinder the reaction, and for example nitrobenzene, methanol, tetrahydrofuran,

N,N-dimethylformamide, toluene and the like or mixture of these solvents may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is 0.1-72 hours, preferably 0.1 to 24 hours.

Compound (I) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 5-1).

Step 5-1 is process to produce condensed compound by reacting compound (4) obtained in the aforesaid step 3 with compound (6).

Amide reaction in this step is performed using compound (4) and carboxylic acid represented by compound (6) or reactive derivative thereof.

Compound (6) or a reactive derivative thereof is used usually at 0.1-100 equivalents, preferably 0.1-3 equivalents.

As "reactive derivative" of compound (6), for example mixed acid anhydride, active ester, active amide and the like can be nominated, and these can be obtained by process in accordance with for example WO98/05641.

In the aforesaid reaction, when carboxylic acid represented by compound (6) is used, for example carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, diphenyl phosphoryl diazide, dipyridyl disulphide-triphenylphosphine and the like, are preferred and reaction is preferably in the presence of condensing agent such as carbonyldiimidazole and the like.

The quantity of the aforesaid condensing agent used is not limited closely, but usually is 0.1-100 equivalents, preferably 0.1-10 equivalents with respect to compound (6).

Reaction is usually carried out in inert solvent, and, as the aforesaid inert solvent, for example tetrahydrofuran, N,N-dimethylformamide, 1,4-dioxane, benzene, toluene, methylene chloride, chloroform, carbon tetrachloride, 1,2-dichloromethane, pyridine and the like or mixture of these solvents may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is between 0.1-72 hours, preferably from 30 minutes to 24 hours.

Moreover, the aforesaid reaction may be performed in the presence of base and condensation assistant in order that the reaction proceed smoothly.

As base, 4-dimethylaminopyridine, triethylamine and the like may be proposed.

The quantity of the aforesaid base used is 0.1-100 equivalents, preferably 0.1-1 equivalents with respect to 1 mole of carboxylic acid represented by compound (6) or reactive derivative thereof usually.

As condensation assistant, N-hydroxybenzotriazole hydrate, N-hydroxy succinimide and the like may be proposed.

The quantity of the aforesaid condensation assistant used is 1-100 equivalents, preferably 1-5 equivalents with respect to 1 mole of carboxylic acid represented by compound (6) or reactive derivative thereof usually.

In the aforesaid reaction, when amino group or imino group which does not participate in reaction in reaction materials is present, preferably it is suitably protected with protecting group of amino group or imino group, and thereafter, it is reacted, and the aforesaid protecting group of said amino group or imino group is eliminated after reaction.

Condensed compound obtained in this way can be subjected to next step without being isolated and purified or can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 5-2).

Step 5-2 is process to produce compound (I-0) by reacting condensed compound obtained in the aforesaid step 5-1.

In this step cyclisation reaction can be performed by process in accordance with literature (for example, process described in Tetrahedron, Vol 57 Number 9, pp 1793-1800, 2001 or the like) or



a process based on this, or a combination of these and a conventional procedure.

When p-toluenesulfonic acid is used in cyclisation reaction, amount of p-toluenesulfonic acid is usually 0.1-100 equivalents, preferably 0.1-1 equivalents.

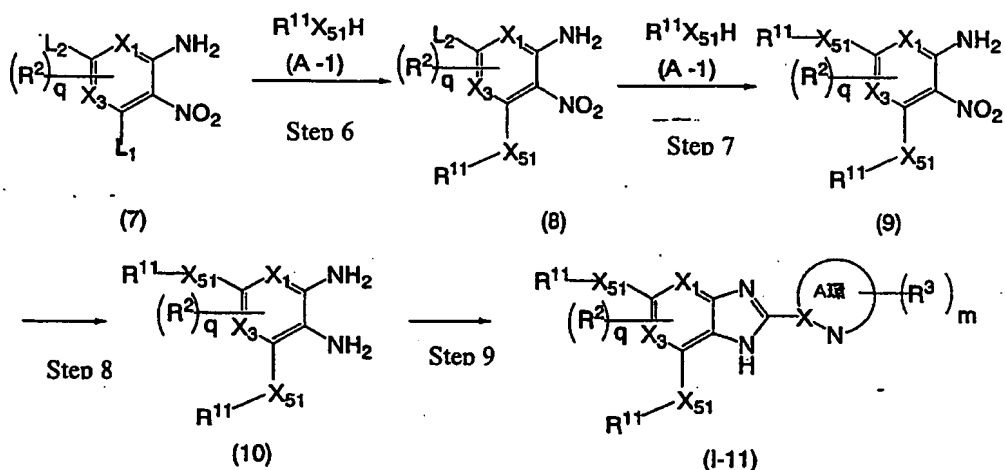
The reaction solvent which is used is not restricted in particular in reaction in this step, provided it does not hinder the reaction, and for example toluene, N,N-dimethylformamide, 1,4-dioxane, N-methylpyrrolidinone and the like or mixture of these solvents may be proposed.

The reaction temperature is 0 to 200 degrees, preferably room temperature to reflux temperature of reaction solvent.

The reaction time is usually 0.1 hours to 72 hours, preferably from 30 minutes to 12 hours.

Compound (I-0) in accordance with this invention obtained in this way may be used without isolation and refinement, or can be isolated and purified by using well-known isolation and separation means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

Compound (I-11) in accordance with this invention can be produced by the following process.



(wherein,  $L^1$ ,  $L^2$  denotes leaving group such as halogen or the like; each symbol has the same definitions as aforesaid.

(Step 6).

This step is process to produce compound (8) by reacting compound (7) with compound (A-1) in the presence of base. More specifically, as L<sup>1</sup>, L<sup>2</sup>, for example, halogen such as fluorine, chlorine and bromine or the like may be proposed.

Amount of compound (A-1) used differs depending on compound and kind of solvent, other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (7).

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used, in this step, any base which produces compound (8), in reaction of compound (7) and compound (A-1), for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

As the reaction solvent which is used, inert solvent may be proposed, and it is not restricted in particular so long as it does not hinder the reaction. and as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0-250°C in this step.

The reaction time is usually 0.1-72 hours, preferably 0.1-5 hours in this step.

Compound (8) obtained in this way can be subjected to next step without being purified and refined, or it may be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 7).

This step is process to produce compound (9) by reaction of compound (8) with compound (A-1) used in the aforesaid step 1 in the presence of base.

This step can be carried out by the same process as in the aforesaid step 6, a process based on this, or a combination of these processes and conventional procedures.

Compound (9) obtained in this way is isolated and refined using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like, or can be subjected to following step without being purified or being isolated and purified it

(Step 8).

This step is process to produce compound (10) by reducing nitro group of compound (9).

This step can be carried out by the same process as in the aforesaid step 3, a method based on this, or a combination of these with conventional procedures.

Compound (10) obtained in this way can be subjected to next step without being isolated and purified or after isolation and purification using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 9).

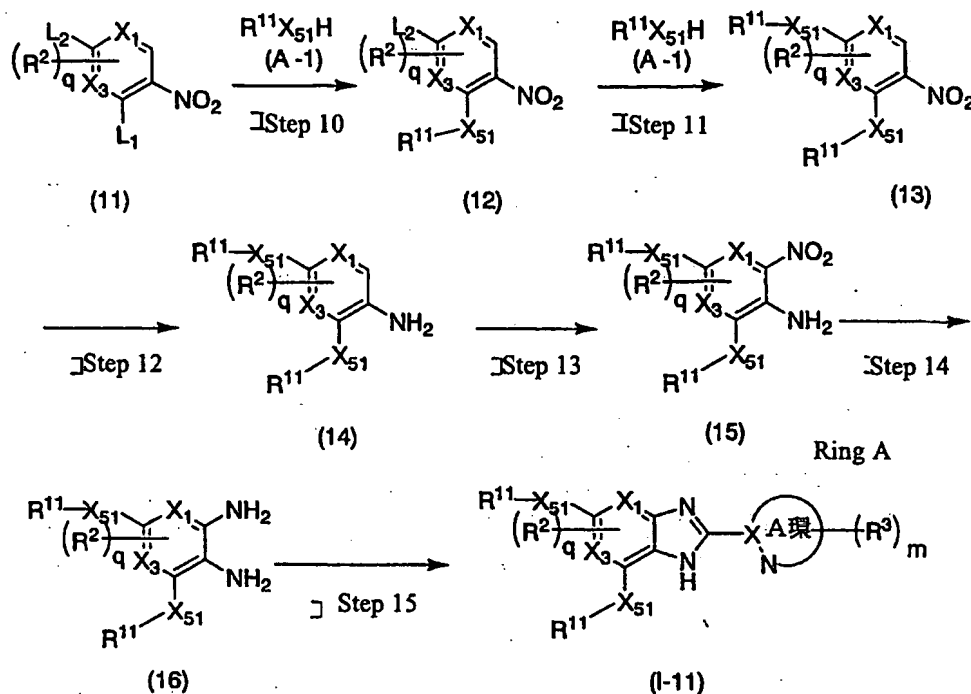
This step is process to produce compound (I-11) in accordance with this invention by reacting compound (10) with aforementioned compound (5) or compound (6).

Reaction of compound (10) and compound (5) can be carried out by the same process as in the aforesaid step 4, a process based on this, or a process combining these and the conventional procedure.

Moreover, reaction of compound (10) and compound (6) can be carried out by the same process as in the aforesaid step 5-1 and 5-2, a process based on this, or a process combining these and the conventional procedure.

Compound (I-11) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Compound (I-11) in accordance with this invention can be produced by the following process.



(wherein,  $L^1$ ,  $L^2$  denotes leaving group such as halogen or the like, and each symbol has the same definitions as aforesaid).

(Step 10).

This step is process to produce compound (12) by reaction of compound (11) and aforementioned compound (A-1).

This step can be carried out by the same process as in aforesaid step 6, a process based on this, or a combination of these and a conventional procedure.

Compound (12) obtained in this way can be subjected to next step without being isolated and purified or can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 11).

This step is process to produce compound (13) by reaction of compound (12) and aforementioned compound (A-1).

This step can be carried out by the same process as in aforesaid step 6, a process based on this, or a combination of these and a conventional procedure.

Compound (13) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 12).

This step is process to produce compound (14) by reducing nitro group of compound (13).

This step can be carried out by the same process as in aforesaid step 3, a process based on this, or a combination of these and a conventional procedure.

Compound (14) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 13).

This step is process to produce compound (15) by introducing nitro group into compound (14) obtained in the aforesaid step.

Nitration in this step process may be performed by process in accordance with literature (for example Synthetic Communications Vol. 31 No. 7, pp 1123-1128, 2001 or the like), or a process based on this, or a combination of these and a conventional procedure. If necessary, said nitration reaction is performed with amino groups in compound (14) protected.

When potassium nitrate is used in nitration, amount of potassium nitrate is usually 0.1-100 equivalents, preferably 0.1-2 equivalents.

Reaction solvent which is used is not restricted in particular provided it does not hinder the reaction in this step, and for example trifluoroacetic acid, trifluoroacetic acid anhydride, hydrochloric acid, sulphuric acid, nitric acid and the like may be proposed.

The reaction temperature is usually 0 degrees to reflux temperature of reaction solvent, preferably room temperature to reflex temperature of solvent.

The reaction time is usually 0.1 to 72 hours, preferably from 30 minutes to 12 hours.

Compound (15) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 14).

This step is process to produce compound (16) by reducing the nitro group which compound (15) contains.

This step can be carried out by the same process as in aforesaid step 3, a process based on this, or a combination of these and a conventional procedure.

Compound (16) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 15).

This step is process to produce compound (I-11) in accordance with this invention by reacting compound (16) and aforementioned compound (5) or compound (6).

Reaction of compound (16) and compound (5) can be carried out by the same process as in aforesaid step 4, a process based on this, or a combination of these and a conventional procedure.

Moreover, reaction of compound (16) and compound (6) can be carried out by the same process as in the aforesaid step 5-1 and 5-2, a process based on this, or a process combining these and the conventional procedure.

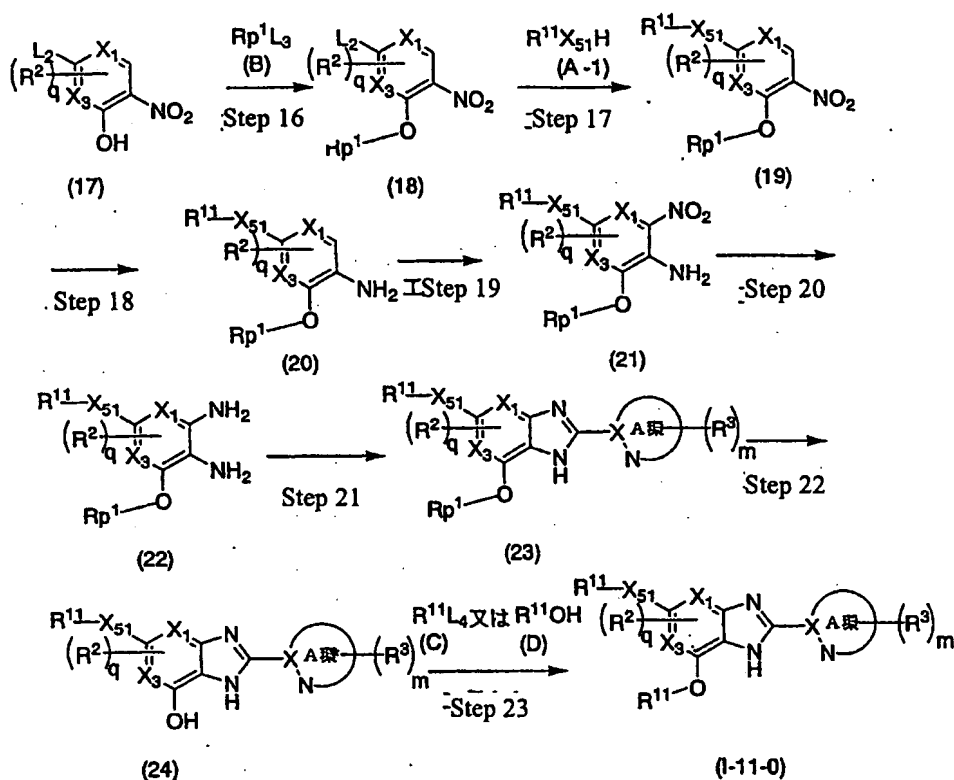
Moreover, it is possible to produce compound (I-11) in accordance with this invention by reacting the aforesaid compound (14) and (6), introducing a nitro group, and finally either reducing said nitro group to amino group, and simultaneously performing cyclisation reaction or carrying out cyclisation separately, in accordance with requirements.

Moreover, amidation, nitration, reduction of nitro group to amine, and cyclisation may be performed by the same method as in step 5-1, step 13, step 3 and step 5-1, a process based on these and a combination of these and a conventional procedure.

Compound (I-11) in accordance with this invention obtained in this way can be isolated and

purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Compound (I-11-0) in accordance with this invention can be produced for example by the following process.



(wherein,  $L^1, L^2, L^3, L^4$  denotes leaving group such as halogen or the like.  $Rp^1$  denotes protecting group of hydroxy. Each symbol has the same definitions as aforesaid).

(Step 16).

This step is reaction to introduce protecting group into compound (17). Introduction of hydroxy protecting group  $Rp^1$  of compound (17) used in this step may be performed as described in the literature, (for example, Protective Groups in Organic Synthesis, T.W. Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

More specifically, for example, as  $Rp^1$ , methoxymethyl, methyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethoxymethyl, 2-(trimethylsilyl) ethyl, tert-butyldimethylsilyl, tert-butyl

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carbonyl and the like may be proposed.

Amount of compound (B) used differs depending on compound and kind of solvent, and other reaction conditions used, usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (17).

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used in this step, any one that produces compound (18) in reaction of compound (17) and compound (B) may be used, but for example cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine, imidazole and the like may be proposed.

Reaction temperature is usually 0 – reflux temperature of reaction solvent, and preferably 0-80°C.

Reaction time is usually 0.1-72 hours, and preferably 0.5-12 hours.

As the reaction solvent which is used, inert solvent is proposed, and is not restricted in particular so long as it does not hinder the reaction, as embodiments for example, pyridine, toluene, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (18) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 17).

This step is process to produce compound (19) by reaction compound (18) and the aforesaid compound (A-1).

This step can be carried out by the same process as in aforesaid step 10, a process based on this, or a combination of these and a conventional procedure.

Compound (19) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization,



reprecipitation, chromatography and the like.

(Step 18).

This step is process to produce compound (20) by reducing the nitro group which compound (19) contains.

This step may be performed by the same process as step 12, process based on this, or a combination of these and a conventional procedure.

Compound (20) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 19).

This step introduces nitro group into compound (20) and is process to produce compound (21).

This step can be carried out by the same process as in aforesaid step 13, a process based on this, or a combination of these and a conventional procedure.

Compound (21) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 20).

This step reduces nitro group of compound (21) and is process to produce compound (22).

This step can be carried out by the same process as in aforesaid step 14, a process based on this, or a combination of these and a conventional procedure.

Compound (22) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 21).

This step is process to produce compound (23) by reacting compound (22) with aforementioned

compound (5) or compound (6).

Reaction of compound (22) and compound (5) can be carried out by the same process as in aforesaid step 4, a process based on this, or a combination of these and a conventional procedure.

Moreover, reaction of compound (22) and compound (6) can be carried out by the same process as in the aforesaid step 5-1 and 5-2, a process based on this, or a process combining these and the conventional procedure.

Compound (23) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 22).

This step is process to produce compound (24) by eliminating protecting group of hydroxy of compound (23).

Elimination of hydroxy protecting group  $Rp^1$  of compound (17) used in this step may be performed by the process described in the literature, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991 and the like), a process based on this, or a combination of these and a conventional procedure, and in this step when  $Rp^1$  is benzyl, for example, said elimination of protecting groups can be carried out by using catalytic hydrogenation using palladium-carbon catalyst.

When palladium hydroxide-carbon catalyst is used in removal of  $Rp^1$ , amount of catalyst is usually 0.01-1000 equivalents, preferably 0.1-10 equivalents.

Reaction solvent used in this step is not restricted in particular provided it does not hinder the reaction, for example methanol, ethanol and the like may be proposed.

The reaction temperature is usually room temperature to reflux temperature of reaction solvent, preferably room temperature to 100 degrees.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 12 hours.

Compound (24) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement

means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 23).

This step is process to produce compound (I-2) in accordance with this invention by step of reacting compound (24) and compound (C) (step 23-1) or step of reacting compound (24) and compound (D) (step 23-2).

(Step 23-1).

As L<sup>4</sup> in compound (C), for example, halogen atom such as chlorine, bromine, iodine or the like may be proposed.

Amount of compound (C) used differs depending on compound and kind of solvent, and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (24).

The reaction in this step is performed in the presence of base. Amount of base used differs depending on compound used, kind of solvent and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (24).

As the base which is used, in reaction of compound (24) and compound (C), any which produced compound (I-2) may be used, but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

As the reaction solvent which is used, inert solvent may be proposed, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0-150°C in this step.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 5 hours in this step.

Compound (I-2) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the

like.

(Step 23-2).

This step is process to produce compound (I-2) in accordance with this invention by reacting compound (24) obtained in the aforesaid step and compound (D) and carrying out protection, deprotection in accordance with requirements.

Reaction of compound (24) and compound (D) can be carried out by so-called Mitsunobu Reaction, in the presence of phosphine compound and azo compound, in accordance with literature (for example Mitsunobu O. et al. "The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products", Synthesis, Vol. 1, 1981 p 1-28), a process based on this or a combination of these with conventional procedure.

Amount of alcohol compound (D) used in this step is usually 0.5-10 equivalents, more preferably 1-3 equivalents with respect to 1 equivalent of compound (24).

As the phosphine compound used in this step, usually for example triphenylphosphine, triethyl phosphine and the like may be proposed.

The amount of phosphine compound used is usually 0.5-10 equivalents, and preferably 1-3 equivalents, for 1 equivalent of compound (24).

As the azo compound which is used, for example diethylazo dicarboxylate, diisopropyl azo dicarboxylate and the like may be proposed.

Amount of azo compound is usually 0.5-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (24).

The reaction time is usually 1-48, preferably 4-12 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 15-30°C in this step.

As the reaction solvent used in this step, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example tetrahydrofuran, toluene and the like may be proposed.

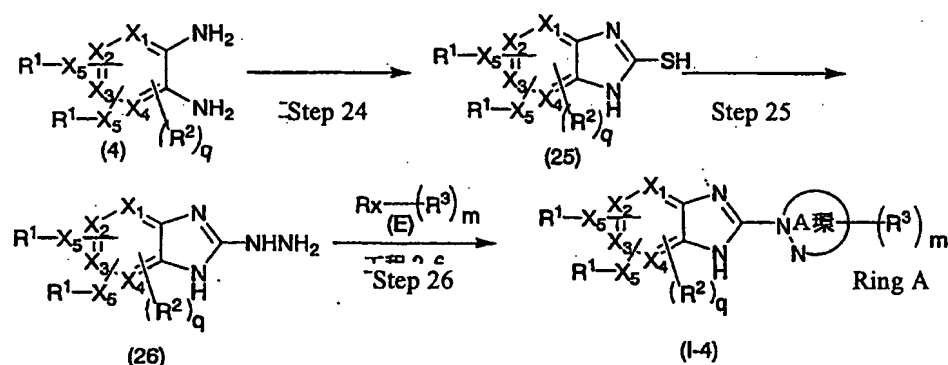
Moreover, it is possible to produce compound (I-11-0) in accordance with this invention by

reacting the aforesaid compound (20) and (6) then introducing a nitro group, and finally, reducing said nitro group to amino group at the same time as it is cyclised, or if necessary, performing cyclisation reaction separately.

Moreover, amidation of compound (20) and compound (6), nitration, nitro group reduction to amino group and cyclisation reaction may be performed by the same processes as in step 5-1, step 13, step 3 and step 5-1, by processes based on these, or on combinations of these and conventional procedures.

Compound (I-11-0) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Of the compounds (I) in accordance with this invention, the compounds (I-4) in which X is nitrogen atom may be produced by the following process.



(wherein,  $Rx$  denotes 1-6C alkyl that has 2 halogen atoms, aldehyde, ester, CN or their equivalents, and the other symbols has the same the aforesaid meaning).

(Step 24).

This step is process to produce compound (25) from compound (4).

This reaction may be performed in the presence of base by process in accordance with literature (for example Indian J. Chem. Sect. B, 32, 2;1993, 262-265) or a process based on this, or a combination of these and a conventional procedure.

For example, when it is reacted using sulfur dioxide, amount of the sulfur dioxide which is used

is usually 0.1-500 equivalents, preferably 0.5-10 equivalents.

As the base which is used, in reaction with compound (4), if it is one which produces compound (25), any kind of one may be used, but for example sodium hydroxide, sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

The reaction time is usually 1-48 hours, preferably 4-12 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0 to reflux temperature of solvent in this step.

As the reaction solvent used in this step, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example ethanol, water, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (25) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 25).

This step produces compound (26) using compound (25). Reaction in this step can be performed using hydrazine monohydrate process in accordance with literature (for example, Indian J. Chem. Sect. B, EN, 32, 2;1993, 262-265) or a process based on this, or a combination of these and a conventional procedure.

Amount of the hydrazine monohydrate which is used is usually 0.1-1000 equivalents, preferably 1-100 equivalents.

The reaction time is usually 1-48 hours, preferably 4-24 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0 to reflux temperature of solvent in this step.

Preferably reaction is carried out with absence of solvent in this step, but a reaction solvent may be used provided it does not hinder the reaction, as embodiments of the reaction solvent, for

example ethanol, water, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (26) obtained in this way is isolated and refined by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like, or it can be subjected to following step without being isolated and purified.

(Step 26).

This step is process to produce compound (I-4) in accordance with this invention by reacting compound (26) and compound (E).

Reaction in this step may be performed by process in accordance with literature (for example Indian J. Chem. Sect. B, EN, 32, 2;1993, 262-265 or the like) or a process based on this, or a combination of these and a conventional procedure.

When for example pyrazole is formed, it can be synthesised by carrying out reaction using tetramethoxypropane.

Amount of tetramethoxy propane used is usually 0.1-500 equivalents, preferably 0.5-100 equivalents.

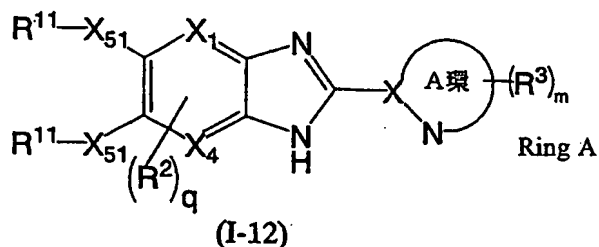
The reaction time is usually 1-48 hours, preferably 4-12 hours in this step.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably 0 degrees to reflux temperature of solvent in this step.

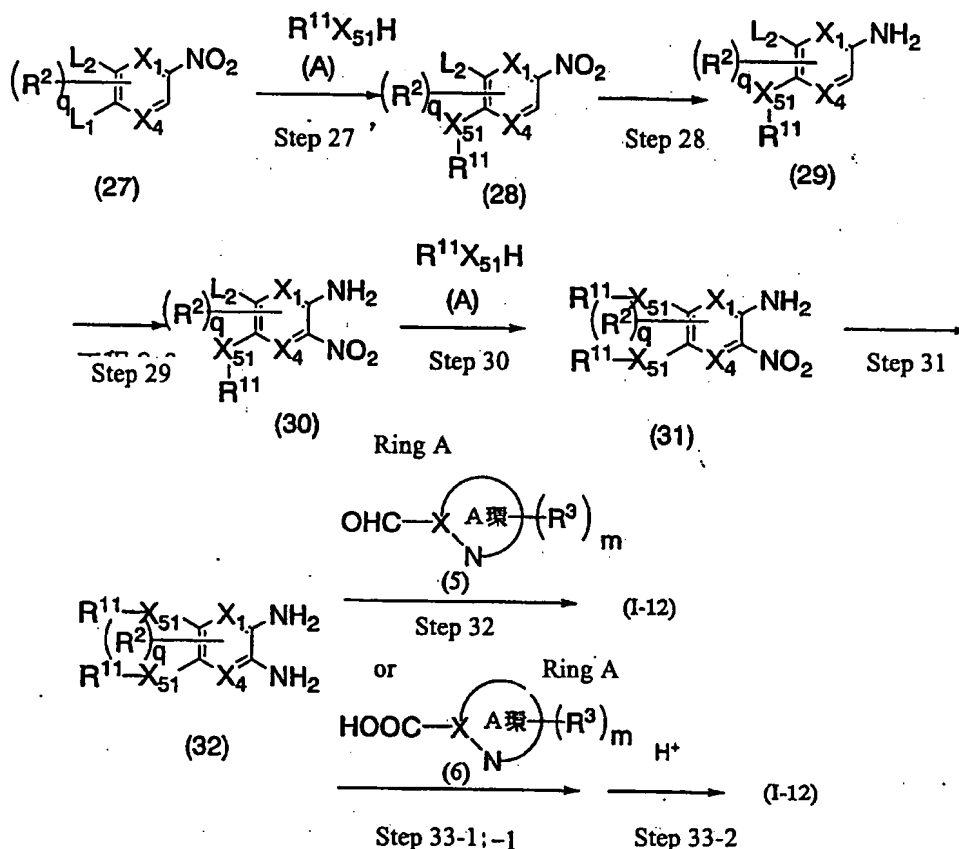
As the reaction solvent used in this step, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example, water, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

Compound (I-4) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Compound (I-12) in accordance with this invention represented by



(each symbol is the same as above) may be produced for example by the following process.



(wherein  $L^1$ ,  $L^2$  denote a leaving group such as halogen, and the other symbols are same as above).

(Step 27).

This step is process to produce compound (28) by reacting compound (27) and the aforesaid compound (A-1) in the presence of base. As  $L^1$ ,  $L^2$ , more specifically, halogen such as fluorine, chlorine and bromine or the like may be proposed.



Amount of compound (A-1) used differs depending on the compound used, the kind of solvent, and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (27).

Amount of base used differs depending on compound used, kind of solvent and other reaction conditions, it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base which is used in this step, if it is one which produces compound (28) by reaction of compound (27) and compound (A-1), any kind may be used, but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium-tert butyrate, triethylamine and the like may be proposed.

As the reaction solvent which is used, inert solvent may be proposed, it is not restricted in particular so long as there is no hindrance of the reaction, as embodiments for example, pyridine, toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to 150 degrees in this step.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 5 hours in this step.

Compound (28) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 28).

This step is process to produce compound (29) by reducing nitro group of compound (28) obtained in the aforesaid step. As for reductive reaction which is used, process well-known to a person skilled in the art is used in this step.

As the reductive reaction used in this step, as embodiments for example, catalytic reduction method using hydrogen, formic acid, ammonium formate, hydrazine hydrate and palladium, platinum, nickel catalyst, reduction method using methanol and tin chloride, catalytic reduction method using hydrochloric acid, ammonium chloride and iron, and the like may be proposed.

In this step, when 10 % palladium-carbon catalyst is used in reduction of nitro group, amount of 10 % palladium-carbon catalyst is usually 0.01-10 equivalents, more preferably 0.1-1 equivalents.

Reaction solvent which is used is not restricted, provided it does not hinder the reaction in reaction in this step, for example methanol, ethanol, tetrahydrofuran, N,N-dimethylformamide and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 12 hours.

Compound (29) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 29).

This step is process to produce compound (30) by introducing nitro group into compound (29) obtained in the aforesaid step.

Nitration in this step may be performed by process in accordance with literature (for example, Synthetic Communication Vol. 31 issue 7, pp 1123-1128, 2001 or the like), or a process based on this, or a combination of these and a conventional procedure, if necessary after adding protecting group to aniline.

When potassium nitrate is used in nitration, amount of potassium nitrate is usually 0.1-100 equivalents, preferably 0.1-1 equivalents.

Reaction solvent used in this step is not restricted in particular provided it does not hinder the reaction, for example trifluoroacetic acid, trifluoroacetic anhydride, hydrochloric acid, sulphuric acid, nitric acid and the like may be proposed.

The reaction temperature is usually 0°C to reflux temperature of reaction solvent, preferably room temperature to reflux temperature of reaction solvent.

Usually the reaction time is 0.1-72 hours, preferably 30 minutes to 12 hours.

Compound (30) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 30).

This step is process to produce compound (31) by reacting compound (30) obtained in the aforesaid step and the aforesaid compound (A-1).

This step may be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure, if necessary after adding aniline protecting group.

Compound (31) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 31).

This step is process to produce compound (32) by reducing nitro group of compound (31) obtained in the aforesaid step 30.

The reaction can be carried out by the same process as in aforesaid step 8, a process based on this, or a combination of these and a conventional procedure in this step.

Compound (32) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 32).

This step is process to produce compound (I-2) in accordance with this invention by reacting compound (32) obtained in the aforesaid step 31 and compound (5).

The reaction can be carried out by the same process as in aforesaid step 4, a process based on this, or a combination of these and a conventional procedure in this step.

Compound (I-2) in accordance with this invention obtained in this way can be isolated and

purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 33-1)

This step is process to produce condensed compound by reacting compound (32) obtained by aforesaid step 31 with compound (6).

The reaction can be carried out by the same process as in aforesaid step 5-1, a process based on this, or a combination of these and a conventional procedure in this step.

Condensed compound obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(33-2).

This step is process to produce compound (I-12) in accordance with this invention by cyclization reaction of condensed compound obtained in the aforesaid step 33-1.

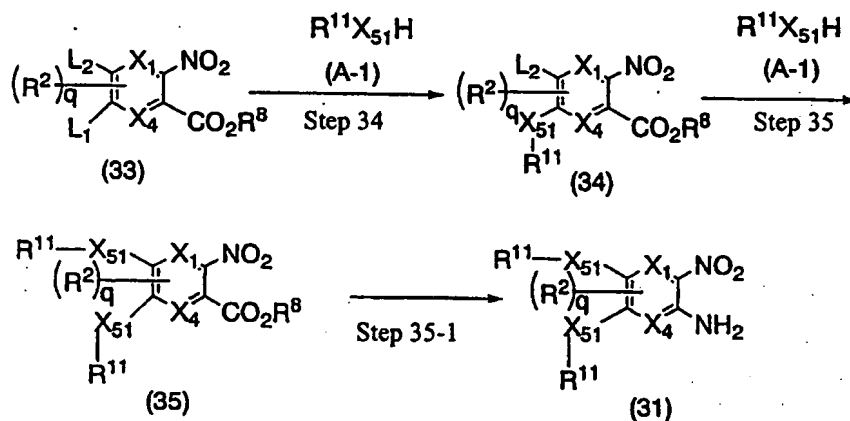
Cyclization reaction can be carried out by the same process as in aforesaid step 5-2, a process based on this, or a combination of these and a conventional procedure in this step.

Moreover, compound (I-11) in accordance with this invention may be produced by reacting the aforesaid compound (29) and (6) then introducing nitro group, and reducing said nitro group to amino group at the same time as cyclization, or if necessary performing cyclization reaction separately, moreover, reacting with compound (A) before cyclization or after cyclization.

Moreover, amidation of compound (29) and compound (6), nitration, reduction of nitro group to amine group, reaction with compound (A) and cyclization reaction may be performed by the same processes as in step 5-1, step 13, step 3, step 30 and step 5-1 respectively, a process based on this or a combination of these processes and the conventional procedure.

Compound (I-12) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Moreover, it is possible to produce compound (I-12) in accordance with this invention by using compound (31) in accordance with the following process.



(wherein, each symbol is the same as above).

(Step 34).

This step is process to produce compound (34) by reacting compound (33) and the aforesaid compound (A-1). In this step, the reaction can be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure.

Compound (34) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 35).

This step is process to produce compound (35) by reacting compound (34) and the aforesaid compound (A-1). In this step, the reaction can be carried out by the same process as in aforesaid step 30, a process based on this, or a combination of these and a conventional procedure.

Compound (35) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 33-1).

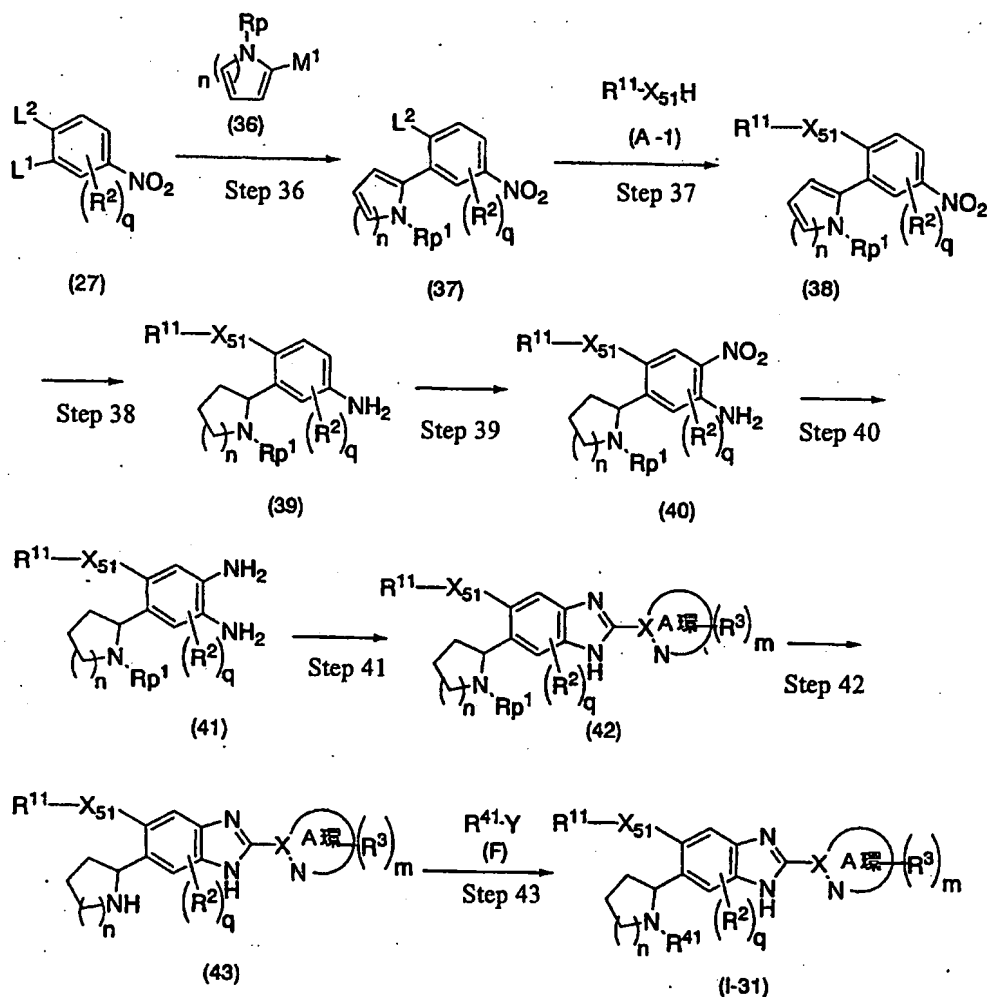
This step is process for producing compound (31) by converted the C(O)OR<sup>8</sup> of compound (35) obtained in the aforesaid step 35 into amino group, for example so-called Curtius transfer  
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reaction may be proposed.

The reaction can be carried out the same process as the step 48 given later, a process based on this or a combination of these processes and the conventional procedure.

Compound (31) obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

Using the obtained compound (31), and using the aforesaid step 31, 32, 33-1 or 33-2, compound (I-12) in accordance with this invention may be produced.



(wherein,  $n$  denotes 1 or 2, and  $Y$  denotes leaving group, and the other symbols are the same as above)

(Step 36)

This step is process for producing compound (37) by reacting the compound (27) mentioned above and compound (36) in the presence of base and metal catalyst.

As  $L^1$  and  $L^2$ , for example, halogen such as fluorine, chlorine, bromine, iodine or the like may be proposed.

Any kind of  $M^1$  may be used as long as it produces compound (37) in the reaction of compound (27) and compound (36), but as embodiments for example tin, boron acid, borate ester and the like trialkyl ester may be proposed. As compound (36), for example, trimethyl-(pyridin-2-yl) tin or 1-(tert butoxycarbonyl) pyrrole-2-boron acid and the like may be proposed.

As compound (36), when trimethyl-(pyridin-2-yl) tin is used, for example, a process using so-called Stille reaction may be proposed.

Moreover, as compound (36), when 1-(tert butoxycarbonyl) pyrrole-2-boron acid is used, for example, a process using so-called Suzuki reaction may be proposed.

Amount of compound (36) used differs depending on the compound and the kind of solvent, other reaction conditions, but it is usually 0.1-50 equivalents with respect to 1 equivalent of compound (27), preferably 0.2-10 equivalents.

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the base used in this step, any kind may be used as long as it produces compound (37) in the reaction of compound (27) and compound (36), but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium t-butoxide, triethylamine and the like may be proposed.

Amount of metal catalyst used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.01-10 equivalents, preferably 0.05-5 equivalents.

As metal catalyst used in this step, any type may be used as long as it produces compound (37) in the reaction of compound (27) and compound (36), and for example tetrakis triphenylphosphine palladium, dichloro bis triphenyl phosphine palladium, dichloro (1,1'-bis (dichlorophosphino) ferrocene) palladium or the like may be proposed.

The reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, for example ethylene glycol dimethylether, water, toluene, tetrahydrofuran, N,N-dimethylformamide, 1,4-dioxane, benzene, acetone and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1-72 hours, preferably 30 minutes to 12 hours.

The compound (37) obtained in this way can be subjected to next step without being purified or being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 37).

This step is process for producing compound (38) by reacting compound (37) and the aforesaid compound (A-1).

In this step, the reaction can be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure.

Compound (38) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 38).

This step is process for producing compound (39) by reducing the hetero aromatic ring and nitro group of compound (38) with metal catalyst under hydrogen atmosphere, and in accordance with requirements introducing protecting group.

Amount of reducing agent used is usually 0.01-10 equivalents, preferably 0.1-1 equivalents.

The reducing agent used in this step can be any as long as it produces compound (39) from compound (38), but for example 10 % platinum-carbon, platinum-black or the like may be proposed.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder



the reaction, and for example methanol, ethanol, tetrahydrofuran, 1,4-dioxane, ethyl acetate and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1-72 hours, preferably 0.5-12 hours.

Usually reaction pressure in this step is normal pressure to 100 atmosphere, preferably normal pressure to 20 atmosphere.

Compound (39) obtained in this way can be subjected to next step without being purified or isolated or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 39).

This step is process for producing compound (40) by introducing nitro group into compound (39). The reaction in this step can be carried out by the same method as in the aforesaid step 29 or process based on this, or a combination of these and a conventional procedure. Rp<sup>1</sup> can be converted in accordance with requirements.

Compound (40) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 40).

This step is process for producing compound (41) by reducing the nitro group of compound (40). The reaction in this step can be carried out by the same process as in aforesaid step 31 or process based on this, or a combination of these and a conventional procedure.

Compound (41) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 41).

This step is process for producing compound (42) by reacting compound (41) and the aforesaid compound (5), or for producing compound (42) by reacting compound (41) and the aforesaid compound (6) and thereafter by subjection to cyclization reaction.

Reaction of compound (41) and the aforesaid compound (5) can be carried out by the same process as in aforesaid step 32 or process based on this, or a combination of these and a conventional procedure.

Moreover, the reaction of reacting compound (41) and the aforesaid compound (6), and thereafter subjecting to cyclization reaction, can be carried out by the same process as in the aforesaid step 33-1 and 33-2, a process based on this, or a process combining these and the conventional procedure.

Compound (42) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 42).

This step is for producing compound (43) by removing the protecting group  $Rp^1$  of the amino group of the obtained compound (42).

The process of elimination of the protecting group  $Rp^1$  of amino group can be carried out by the process described above, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

Compound (43) obtained in this way can be subjected to next step without being purified or isolated or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 43).

This step is process to produce compound in accordance with this invention (1-3) by reacting compound (43) and compound (F). Introduction of protecting group  $R^4$  of amino group used in this step may be performed by the process described above (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

As R<sup>4</sup>, for example, alkyl, alkyl amide, carbamoyl, alkylcarbamoyl, alkyl carbamate and the like may be proposed.

As compound (F), for example, acetic anhydride, anhydrous trifluoroacetic acid, propionic acid, chloroacetic acid, acrylic acid ethyl ester, methane sulphonyl chloride, benzyl bromide and the like may be proposed.

Amount of compound (F) used differs depending on the compound used and the kind of solvent, other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (43).

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, and for example dichloromethane, chloroform, tetrahydrofuran, acetonitrile, dimethylformamide, benzene, acetone, ethanol, 2-propanol and the like are nominated.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1 to 72 hours, and preferably from 30 minutes to 12 hours.

Moreover, the aforesaid compound (39) and (6) are reacted, thereafter, nitro group is introduced, and finally cyclisation is carried out simultaneously to the reduction of the said nitro group to amino group, or in accordance with requirements cyclisation reaction is separately carried out, and thereby the compound in accordance with this invention (1-31) can be produced.

Moreover, the amidation of compound (39) and compound (6), nitration and reduction from nitro group to amino group and cyclisation reaction can be carried out respectively by the same process as in the aforesaid step 5-1, step 13, step 3 and step 5-1, processes based on these, or processes combining these and the conventional procedure.

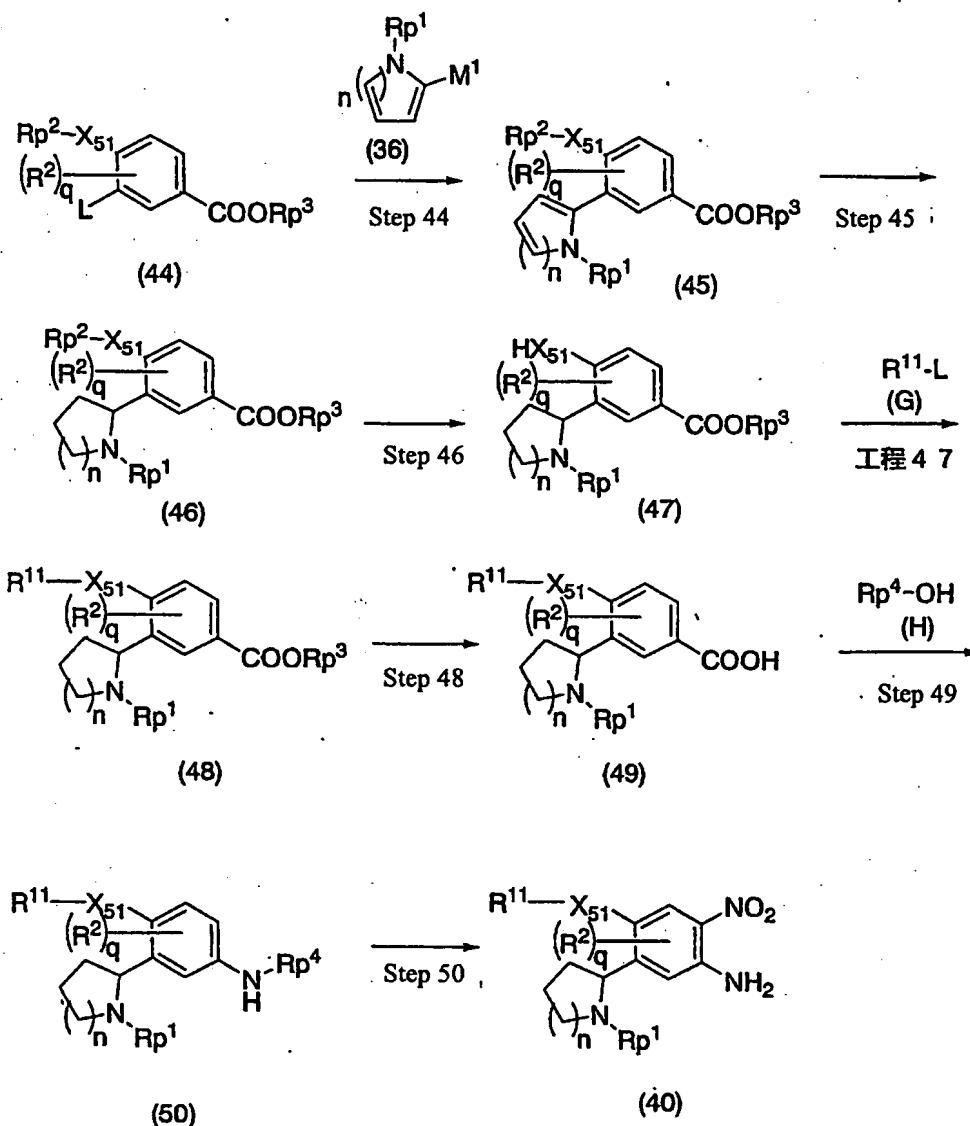
Compound in accordance with this invention obtained in this way (1-31) can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

Moreover, in compound (42), when the protecting group Rp<sup>1</sup> of amino group comes under

desired  $R^4$ , the compound (42) is the compound in accordance with this invention without thereafter carrying out steps 42 and 43.

Moreover, when compound (43) is desired compound, compound (43) comprises compound in accordance with this invention without carrying out step 43.

The compound in accordance with this invention (1-31) can be produced by following process.



(wherein,  $Rp^2$ ,  $Rp^3$  and  $Rp^4$  respectively denote protecting group, and  $L$  denotes leaving group, and the other symbols are the same as above).

(Step 44).

This step is a processes to produce compound (45) by reacting compound (44) and the aforesaid compound (36). Rp2 denotes protecting group of X<sub>5</sub>, and as embodiments for example, methoxymethyl, methyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethoxymethyl, 2-(trimethylsilyl) ethyl, tert-butyldimethylsilyl, tert-butyl carbonyl and the like may be proposed. Moreover, Rp3 denotes protection of carboxyl, and as embodiments for example methoxymethyl, methyl, ethyl, tert-butyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethyl, tert-butyldimethylsilyl and the like may be proposed. Rp4 denotes inert alkyl, and as embodiments for example, methyl, ethyl, tert-butyl, benzyl, 4-methoxy-benzyl, 2-(trimethylsilyl) ethyl and the like may be proposed. The reaction in this step can be carried out by the same process as in aforesaid step 36, a process based on this, or a combination of these and a conventional procedure. Compound (45) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 45).

This step is process for producing compound (46) by reducing the hetero aromatic ring of compound (45) obtained in aforesaid step with metal catalyst under hydrogen atmosphere.

Amount of reducing agent used is usually 0.01-10 equivalents, preferably 0.1-1 equivalents.

The reducing agent used in this step can be any as long as it produces compound (46) from compound (45), but for example 10 % platinum-carbon, platinum-black or the like may be proposed.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, and for example methanol, ethanol, tetrahydrofuran, 1,4-dioxane, ethyl acetate and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

The reaction time in this step is usually 0.1-72 hours, preferably 0.5-12 hours.

Usually reaction pressure in this step is normal pressure to 100 atmosphere, preferably normal pressure to 20 atmosphere.

Compound (46) obtained in this way can be subjected to next step without being purified or isolated or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 46).

This step is process to produce compound (47) by removing the protecting group Rp2 of compound (46). The elimination of the protecting group in this step can be carried out by the process described above, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure. When the Rp2 is methoxymethyl, for example, said elimination of protecting groups can be carried out by using trifluoroacetic acid and the like.

When trifluoroacetic acid is used for the removal of Rp<sup>1</sup>, amount of catalyst is usually 0.01-1000 equivalents, preferably 0.1-10 equivalents.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, for example chloroform and the like may be proposed.

Usually the reaction temperature is room temperature to reflux temperature of the reaction solvent, preferably room temperature to 100°C.

Usually the reaction time is 0.1-72 hours, preferably from 30 minutes to 12 hours.

Compound (47) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like. Rp<sup>1</sup> can be converted in accordance with requirements.

(Step 47).

This step is process to produce compound (48) by reacting compound (47) and compound (G). Wherein, L denotes leaving group, and the groups same as in the aforesaid L<sup>1</sup> and L<sup>2</sup> may be proposed. As compound (G), for example, benzyl bromide, 4-fluoro-benzonitrile, 4-fluoro-benzaldehyde and the like may be proposed. In this step, the reaction can be carried out by the same process as in aforesaid step 27, a process based on this, or a combination of these and a conventional procedure. Compound (48) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known

separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography.

(Step 48).

This step is process to produce compound (49) by removing the protecting group Rp3 of the carboxyl which compound (48). As protecting group of the carboxyl which compound (48), any kind can be used as long as it acts as protecting group of carboxyl in the aforesaid steps 44-47 and it can be readily eliminated in step 48, and for example lower alkyl containing straight chain or branched chain such as methyl, ethyl, tert-butyl and the like, halogeno lower alkyl such as 2-iodo ethyl, 2,2,2-trichloroethyl and the like, allyl lower alkenyl such as 2-propenyl, 2-methyl-2-propenyl and the like, aralkyl and the like such as benzyl, para methoxy-benzyl and the like are nominated.

The introduction and removal process of protecting group Rp3 of such carboxyl can be carried out by the process described in literature (for example, Protective Groups in Organic Synthesis, T.W. Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure. When the Rp2 is methoxymethyl, for example, said elimination of protecting groups can be carried out by using trifluoroacetic acid and the like.

Compound (49) obtained in this way can be subjected to next step without being isolated and purified or after being isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

(Step 49).

This step is process to produce compound (50) by reacting compound (49) and compound (H), and it is so-called Curtius rearrangement reaction and can be carried out using phosphoric acid azide compound in the presence of base and alcohol compound (17-1) process in accordance with literature (for example, Tetrahedron, vol. 31, 1974, pp. 2151-2157 etc), a process based on this, or a combination of these and a conventional procedure.

Amount of alcohol compound (H) used differs depending on the compound and the kind of solvent, other reaction conditions used, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents with respect to 1 equivalent of compound (49).

Amount of base used differs depending on the compound used, the kind of solvent, and other reaction conditions, but it is usually 0.1-20 equivalents, preferably 0.5-5 equivalents.

As the phosphoric acid azide compound used in this step, any kind may be used as long as it produces compound (50) in the reaction of compound (49) and compound (H), but for example diethyl phosphoric acid azide, diphenyl phosphoric acid azide and the like may be proposed.

As the base used in this step, any kind may be used as long as it produces compound (50) in the reaction of compound (49) and compound (H), but for example sodium hydride, cesium carbonate, sodium carbonate, potassium carbonate, potassium phosphate, potassium acetate, potassium t-butoxide, triethylamine and the like may be proposed.

Reaction solvent used in this step is not restricted in particular providing that it does not hinder the reaction, for example toluene, tetrahydrofuran, methylene chloride, chloroform, 1,4-dioxane, benzene and the like may be proposed.

The reaction temperature in this step is usually 0°C to reflux temperature of reaction solvent, preferably from room temperature to 150°C.

Usually the reaction time in this step is 0.1-72 hours, preferably 30 minutes-12 hours.

Compound (50) obtained in this way can be subjected to next step without being purified it made of or isolation to be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like.

(Step 50).

This step is process to produce aforesaid compound (40) by introducing nitro group into compound (50). The reaction in this step can be carried out by the same process as in the aforesaid step 29, a process based on this, or a combination of these and a conventional procedure.

The compound (40) obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, crystallization, solvent extraction, reprecipitation, chromatography and the like, or without being isolated and purified, and the compound in accordance with this invention (I-3) can be produced by the process of the aforesaid steps 40-43.

Moreover, the amidation of compound (50) and compound (6), nitration and reduction from nitro group to amino group and cyclisation reaction can be carried out respectively by the same process as in the aforesaid step 5-1, step 13, step 3 and step 5-1, processes based on these, or processes



combining these and the conventional procedure. The elimination of Rp4 can be carried out by the process described above, (for example, Protective Groups in Organic Synthesis, T.W, Green, 2nd edition, John Wiley and Sons, 1991), a process based on this, or a combination of these and a conventional procedure.

The novel 2-heteroaryl substituted benzimidazole derivatives put forward by this invention can exist as pharmacologically acceptable salts, and, the aforesaid salts can be produced in accordance with conventional procedures using the compound (I-0) in accordance with this invention and compounds (I-1), (I-11), (I-12), (I-2), (I-11-0), (I-31), and (I-4) included in compound (I-0).

In an embodiment, when the aforesaid compounds (I-0), (I-1), (I-11), (I-12), (I-2), (I-11-0), (I-31), and (I-4) have basic group originated from amino group, pyridyl group, and the like in the molecule, it can be converted to corresponding pharmacologically acceptable salt by treating the aforesaid compound with acid.

As the aforesaid acid addition salt, the acid addition salts which are for example hydrohalide salt such as hydrochloride, hydrofluoride, hydrobromide, hydroiodide or the like, inorganic salt such as nitrate, perchlorate, sulfate, phosphate, carbonate or the like, lower alkyl sulfonate such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate or the like, aryl sulfonate such as benzensulphonate, p-toluenesulfonate or the like, organic salt such as fumarate, succinate, citrate, tartrate, oxalate, maleate or the like and amino acid salt or the like such as glutamic acid salt, aspartate or the like may be proposed. Moreover, when the compound of this invention has acidic group in the aforesaid group, when for example carboxyl groups are contained, it can be converted to corresponding pharmacologically acceptable salt by treating the aforesaid compound with base.

As the aforesaid base addition salt, salts with alkali metal salt such as sodium, potassium and the like, alkaline earth metal salt such as calcium, magnesium and the like, ammonium salt, organic base such as guanidine, triethylamine, dicyclohexylamine and the like can be nominated. The compound of this invention may be present as free compound or arbitrary hydrate of salts thereof or solvate furthermore.

For the production of drug for prevention or therapy of type II diabetes mellitus or diseases or symptoms related to this, the compound of formula (I) in accordance with this invention can be combined with carrier substance.

The dosage of the compound of formula (I) in accordance with this invention for the therapy or

prevention of course changes according to the nature of the symptoms to be treated, specific compound selected and administration route.

Moreover, it also changes according to the age, body weight and sensitivity of each patient. Generally, the dosage per day as amount of single administration or a plurality of administrations, it is at least from about 0.001 mg to at most about 100 mg per 1 kg in weight and preferably it is from about 0.01 mg to about 50 mg per 1 kg in weight and is more preferably from about 0.1 mg to 10 mg. There may be a case wherein the dosage exceeding this range may be necessary.

As example of appropriate dose of oral administration, as single dosing or plurality of administrations of 2-4 times per day, it is from at least about 0.01 mg to at most 2.0 g. Preferably, the dose range is, with administration of once or twice per day, from about 1.0 mg to about 200 mg. More preferably, the dose range is from about 10 mg to 100 mg by administration of once per day.

When intravenous administration or oral administration is used, typical administration range is from about 0.001 mg to about 100 mg of compound of formula (I) per 1 kg in weight per day (preferably from 0.01 mg to about 10 mg), and more preferably, from about 0.1 mg to 10 mg of compound of formula (I) per 1 kg in weight per day.

As described earlier, the medicinal composition includes compound of formula (I) and pharmacologically acceptable carrier. The term of "composition" includes, directly or indirectly a product formed by combining, compounding or aggregating two or more components, a product formed as a result of dissociation of one or more components, or a product formed as a results of interaction or other types of action between components, as well as active and inert components that constituting the carrier (including pharmaceutically acceptable excipients).

A composition containing compound of formula (I) in a sufficient dose for therapy, prevention of type II diabetes mellitus or delaying of the onset thereof, in combination with pharmacologically permitted carrier, is preferred.

In order to administer the effective amount of compound in accordance with this invention to mammal, more particularly to human, any appropriate administration route can be used. For example, oral, rectal, local, vein, eye, lung, nose or the like can be used. As example of administrative form, there are tablet, troche, powder, suspension, solution, capsule, cream, aerosol or the like, and the tablet for oral is preferred.

For the preparation of oral composition, any kind of vehicle for ordinary drug can be used, and as

such example, there are for example water, glycol, oil, alcohol, flavor additive, preservation charges, coloring agent or the like. When a liquid composition for oral is prepared, for example suspension, elixir agent and solution are proposed, and as carrier, for example, starch, sugar, microcrystalline cellulose, diluent, granulating agent, lubricant, binding agent, disintegrating agent or the like are proposed, when solid body composition for oral is prepared, for example, powder, capsule, tablet or the like are proposed, wherein the solid body composition for oral is preferred.

From ease of administration, tablet and capsule are the most useful oral administration forms. The tablet can be coated with normal aqueous or non-aqueous technique is possible in accordance with requirements.

In addition to aforesaid usual administration forms, the compound in accordance with formula (I) can be administered by release controlling means and/or delivery apparatus in accordance with U.S. patent number 3,845,770, 3,916,899, 3,536,809, 3,598,123, 3,630,200 and 4,008,719.

The medicinal composition suitable for oral administration in accordance with this invention may be capsule, cachets or tablets containing including active ingredient of pre-determined amount, as powder or granule, or as aqueous solution, non-aqueous liquid, water-in-oil emulsion oil-in-water emulsion, respectively. Such composition may be prepared using any process in pharmaceuticals, but in all processes also include a process in which active ingredient and carrier formed from 1 or more essential components are united.

Generally, active ingredient is mixed thoroughly and uniformly with liquid carrier or well-separated solid carrier or both, and thereafter, product is made into a suitable shape in accordance with requirements, and thereby composition is prepared. For example, tablet is prepared by compression and molding, if necessary with 1 or more additional components. Compression tablet is mixed with binding agent, lubricant, inert excipient, surfactant or dispersant in accordance with requirements in a suitable machine and is prepared by compressing active ingredient in shape such as powder and granule or the like freely.

Molded tablet is prepared by forming mixture of moistened compound of powder form and diluent of inert liquid in suitable machine.

Preferably each tablet includes active ingredient in amount of about 1mg to 1g, and each cachet or capsule includes active ingredient in amount of about 1mg to 500 mg.

Example of administrative form of drug of compound of formula (1) is as follows.

Table 1

Suspension for injection (I.M.):

Compound of formula (1)	10 mg/ml
Methyl cellulose	5.0 mg/ml
Tween80	0.5 mg/ml
<u>Benzyl alcohol</u>	<u>9.0 mg/ml</u>

Water used for injection is added to make 1.0 ml.

Table 2

Tablet

Compound of formula (1)	25 mg/tablet
Methyl cellulose	415 mg/tablet
Tween80	14.0 mg/tablet
<u>Benzyl alcohol</u>	<u>43.5 mg/tablet</u>

Total 500 mg.

Table 3

Capsule

Compound of formula (1)	25 mg/capsule
Lactose powder	573.5 mg/capsule
<u>Magnesium stearate</u>	<u>1.5 mg/capsule</u>

Total 600 mg

Table 4

Aerosol

Compound of formula (1)	24 mg per container
Lecithin, NF Liq. Conc.	1.2 mg per container
Trichlorofluoromethane, NF	4.025 mg per container
<u>Dichlorodifluoromethane, NF</u>	<u>12.15 mg per container</u>

The compound of formula (1) may be used combined with other agents used not only for disease and symptoms of type 2 diabetes, but also in therapy of onset of 2 type diabetes mellitus, or its prevention or delay. The said other agent may be administered at the same time as compound of formula (1) or separately, by administration route or dose usually used.

When the compound of formula (1) is used at the same time as 1 or more agent, the medicinal composition which included the compound of formula (I) and the other agent is preferable.

Accordingly, medicinal composition in accordance with this invention includes 1 or more other active ingredients in addition to compound of formula (1). Active ingredient used in combination with compound of formula (1), and administered separately or in the same medicinal composition, are not restricted to following examples.

- (a). bisguanide (for example buformin, metformin, phenformin),
- (b) PPAR agonist (for example troglitazone, pioglitazone, rosiglitazone),
- (c) Insulin,
- (d) Somatostatin,
- (e)  $\alpha$ -glucosidase inhibitor (for example Voglibose, miglitol, acarbose),
- (f) insulin secretion accelerating agent (for example acetohexamide, carbutamide, chlorpropamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide, glyburide, glyhexamide, glypinamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide, nateglinide, repaglinide), and
- (g) DPP-IV (dipeptidyl peptidase IV) inhibitor.

Weight ratio of compound of formula (1) with respect to 2nd active ingredient varies within wide limits, and moreover, depends on the effective dose of each active ingredient. Accordingly, for example, when compound of formula (1) is used in combination with PPAR agonist, weight ratio with respect to PPAR agonist of compound of formula (1) is generally about 1000:1 – 1:1000 and is preferably about 200:1 – 1:200. The combination of compound of formula (1) and other active ingredient is in the aforesaid range, but in all cases, an effective dose of each active ingredient should be used.

The glucokinase activity which compound represented by compound (1) in accordance with this invention shows, and test process thereof are shown in the following.

The excellent glucokinase activation action that compound represented by the aforesaid formula (1) has can be measured by process in accordance with literature (for example, Diabetes Vol. 5 No. 5, pp1671-1677, 1996) or method in accordance with it.

Glucokinase activity is not measured by measuring glucose-6-phosphoric acid directly, but degree of activation of glucokinase is examined by measuring amount of Thio-NADH produced when glucose-6-phosphoric acid dehydrogenase, which is reporter enzyme, produces phosphogluconolactone from glucose-6-phosphoric acid.

The recombinant human liver used in this assay was expressed in E.coli as FLAG fusion protein and was refined with ANTIFLAG M2 AFFINITY GEL (Sigma).

The assay was carried out at 30°C using flat bottom 96-well plate. 69 µl of assay buffer (25mM Hepes Buffer: pH = 7.2, 2mM MgCl<sub>2</sub>, 1mM ATP, 0.5mM TNAD, 1mM dithiothreitol) was discharged, and 1 µl was added of DMSO solution of compound or DMSO control. Thereafter, enzyme mixture (FLAG-GK, 20U/mg6PDH) 20 µl cooled in ice is discharged, and thereafter, 25 mM glucose 10 µl which is substrate is added, and reaction is started (final glucose concentration = 2.5 mM).

After start of reaction, increase of absorbance of 405 nm was measured every 30 seconds for ten minutes, and the increment during the first five minutes was used, and evaluation of compound was carried out. FLAG-GK was added so that absorbance increment in the presence of 1 % DMSO after five minutes was between 0.05-0.1.

OD was measured at each concentration of the evaluation compound, taking the OD value with DMSO control as 100 %. From OD value of each concentration, E<sub>max</sub> (%) and EC<sub>50</sub> (µM) were calculated, and used as index of GK activation ability of compound.

GK activation ability of compound in accordance with this invention was measured by this method. The results thereof are shown in Table 1 (sic).

Table 5

(GK activation ability of the compounds of this invention)

<u>Compound number</u>	<u>E<sub>max</sub> (%)</u>	<u>EC<sub>50</sub> (µM)</u>
Example 67	832	1.4
Example 26	768	2.3
Example 122	664	1.9

As shown in the aforesaid Table 1, the compounds in accordance with this invention have excellent GK activation ability, using E<sub>max</sub> and EC<sub>50</sub> as index.

#### Examples

Hereinafter, this invention is described in greater detail by providing examples. However, this invention is not restricted in any way by these.

#### Preparation Example 1

10 pts. of compound of Production Example 1, heavy magnesium oxide 15 pts. and lactose 75 pts. are uniformly mixed and are made into powder in the form of fine granules or fine powder of 350 micrometer or less. This powder is introduced into capsule container, and capsule is formed.

**Preparation Example 2**

After uniformly mixing 45 pts. of compound of Production Example 1, starch 15 pts, lactose 16 pts, crystalline cellulose 21 pts, polyvinyl alcohol 3 pts. and distilled water 30 pts, the mixture is pulverised and granulated, and dried, then sieved to make granules of diameter of 1410-177  $\mu\text{m}$ .

**Preparation Example 3**

Granule is produced by same process as in Preparation Example 2, and thereafter, calcium stearate 3 pts. with respect to this granule 96 pts. is added, and it is compression-molded, and tablet of a diameter of 10 mm is produced.

**Preparation Example 4**

Crystalline cellulose 10 pts. and calcium stearate 3 pts. are added to 90 pts. of granules obtained by process of Preparation Example 2, and it is compression-molded, and it is formed into tablet of a diameter of 8 mm, thereafter, syrup gelatin - precipitated calcium carbonate mixed suspension is added to this, and sugar coated tablet is produced.

Hereinafter, this invention will be described in greater detail using Preparation Example, Production Example, Reference Example. However, this invention is not restricted in any way by these.

Thin layer chromatograph of the Example used Silicagel60F245(Merck) as plate and UV detector as detection method. Silica gel for as far as column was concerned, and, with WaKogeITM -300C (Wako Jyunyaku), LC-SORBTM SP-B-ODS(Chemco) or YMC-GELTM ODS-AQ120-S50 (Yamamura Institute for Chemical Research) was used as silica gel for reverse phase column.

Meaning of abbreviation in the following Examples is shown below.

i-Bu: isobutyl

n-Bu: n-butyl

t-Bu: t-butyl

Me: methyl

Et: ethyl

Ph: phenyl

i-Pr: isopropyl

n-Pr: n-propyl

CDCl<sub>3</sub>: deuterated chloroform

CD<sub>3</sub>OD: deuterated methanol

DMSO-d<sub>6</sub>: heavy dimethyl sulphoxide

Meaning of abbreviation in nuclear magnetic resonance spectrum is denoted as follows.

s: singlet

d: doublet

dd: double doublet

t: triplet

m: multiplet

br: broad

q: quartet

J: coupling constant

Hz: Hertz.

#### Example 1

##### 2-pyridine-2-yl-5,6-bis (pyridine-3-yloxy)-1H benzimidazole

##### Step 1

##### Synthesis of 3-(2-fluoro-4-nitro-phenoxy)-pyridine

To dimethylformamide 20 ml solution of 3,4-difluoro nitrobenzene 3.18 g were added 3-hydroxypyridine 2.09 g and potassium carbonate 5.52 g, and the reaction liquor was stirred at 90°C for one hour. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1) and the title compound was obtained.

##### Step 2



Synthesis of 5-fluoro-2-nitro-4-(pyridine-3-yloxy)-phenylamine

To 3-(2-fluoro-4-nitro-phenoxy)-pyridine 4.72 g dissolved in methanol 30 ml, 20 % palladium hydroxide-carbon catalyst 1.0 g was added, and the reaction liquor was stirred under a hydrogen atmosphere for five hours. After eliminating the catalyst by filtration, the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To trifluoroacetic acid 40 ml solution of the obtained crude product was added potassium nitrate 1.88 g, and the reaction liquor was stirred at room temperature overnight, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate.

The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 4/1) and the title compound was obtained.

**Step 3**Synthesis of 4,5-bis-(pyridine-3-yloxy)-benzene-1,2-diamine

To dimethylformamide 8 ml solution of 3-(2-fluoro-4-nitro-phenoxy)-pyridine 680 mg were added 3-hydroxypyridine 285 mg and potassium carbonate 829 mg, and the reaction liquor was stirred at 90°C for two hours. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate) and the crude product was obtained. To ethanol 10 ml solution of the obtained crude product, developing Raney nickel catalyst 500 mg was added, and the reaction liquor was stirred under a hydrogen atmosphere for two hours. The catalyst was eliminated by filtration, and the title compound was obtained by eliminating the solvent by distillation under reduced pressure.

**Step 4**Production of 2-pyridine-2-yl-5,6-bis (pyridine-3-yloxy)-1H-benzimidazole

Pyridine-2-carboxaldehyde 0.01 ml was added to nitrobenzene 0.3 ml solution of 4,5-bis-(pyridine-3-yloxy)-benzene-1,2-diamine 30 mg at 120°C, and the reaction liquor was stirred at the same temperature for two hours. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase : water-acetonitrile-0.1% trifluoroacetic acid].

Solvent of the obtained fraction was eliminated by distillation under reduced pressure, and

thereafter, it was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol=20/1), and obtained the title compound as a yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 7.10-7.40 (4H, m), 7.28 (1H, s), 7.38 (1H, ddd, J = 1.2Hz, 4.8 Hz, 7.6 Hz), 7.62 (1H, s), 7.87 (1H, td, J = 7.6Hz, 1.2 Hz), 8.12-8.40 (4H, m), 8.38 (1H, d, J = 7.6 Hz), 8.63 (1H, d, J = 4.8 Hz), 10.8 (1H, brs).

ESI-MS (m/e): 382 (M+H).

#### Example 2

##### 5-(2-hydroxymethyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-2-nitro-4-(pyridine-3-yloxy)-phenylamine obtained in Example 1 (Step 2) and 2-hydroxymethyl-phenol, the title compound was obtained as a colourless solid by the same process as in Example 1, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 4.45 (2H, s), 6.76 (1H, d, J = 8.0 Hz), 7.04 (1H, t, J = 6.8 Hz), 7.08-7.30 (5H, m), 7.30-7.43 (2H, m), 7.86 (1H, td, J = 8.0Hz, 2.4 Hz), 8.18-8.32 (1H, m), 8.22 (1H, s), 7.36 (1H, d, J = 7.6 Hz), 8.62 (1H, d, J = 8.4 Hz), 10.54 (1H, brs).

ESI-MS (m/e): 411 (M+H).

#### Example 3

##### 5-(2-(1-hydroxy-ethyl)-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-(1-hydroxy-ethyl)-phenol, the title compound was obtained as a colourless solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.25-1.34 (6H, m), 4.80-4.96 (1H, m), 7.76 (1H, dd, J = 4.4Hz, 8.0 Hz), 7.02-7.34 (6H, m), 7.38 (1H, t, J = 6.4 Hz), 7.42-7.60 (1H, m), 7.87 (1H, td, J = 7.6Hz, 1.6 Hz), 8.20-8.34 (2H, m), 8.39 (1H, d, J = 7.6 Hz), 8.60-8.64 (1H, m), 10.72 (1H, brs).

ESI-MS (m/e): 425 (M+H).

#### Example 4

##### 5-(2-acetyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-acetyl-phenol, the title compound was obtained as colourless solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.22-2.50 (3H, m), 6.81 (1H, d, J = 8.4 Hz), 7.00-7.45 (4H, m), 7.45-7.95 (5H, m), 8.20-8.35 (2H, m), 8.37 (1H, d, J = 7.6 Hz), 8.60-8.70 (1H, m), 10.49 (1H, brs).

ESI-MS (m/e): 423 (M+H).

#### Example 5

5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-hydroxy-benzonitrile, the title compound was obtained as a straw-coloured solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.80 (1H, t, J = 8.0 Hz), 7.06 (1H, t, J = 7.6 Hz), 7.25-7.35 (2H, m), 7.35-7.7471H, m), 7.56 (1H, d, J = 7.6 Hz), 7.58-7.70 (1H, m), 7.87 (1H, t, J = 7.6 Hz), 8.12-8.25 (1H, m), 8.31 (1H, brs), 8.38 (1H, d, J = 8.0 Hz), 8.58-8.68 (1H, m), 10.80-11.08 (1H, m).

ESI-MS (m/e): 406 (M+H).

**Example 6**5-(3-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-hydroxy-benzonitrile, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 7.02-7.08 (2H, m), 7.14 (1H, d, J = 7.5 Hz), 7.20 (1H, dd, J = 4.4Hz, 7.5 Hz), 7.28-7.36 (3H, m), 7.39 (1H, t, J = 5.9 Hz), 7.42-7.52 (1H, m), 7.88 (1H, dt, J = 1.6Hz, 7.9 Hz), 8.22 (1H, d, J = 3.6 Hz), 8.30 (1H, d, J = 3.6 Hz), 8.39 (1H, d, J = 7.9 Hz), 8.62 (1H, d, J = 5.9 Hz).

ESI-MS (m/e): 406 (M+H).

**Example 7**5-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-hydroxy-benzonitrile, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.84 (2H, d, J = 7.0 Hz), 7.04-7.12 (1H, m), 7.12-7.26 (1H, m), 7.26-7.43 (1H, m), 7.30-7.43 (1H, m), 7.51 (2H, d, J = 7.0 Hz), 7.44-7.76 (1H, m), 7.78-7.90 (1H, m), 8.12-8.21 (1H, m), 8.21-8.30 (1H, m), 8.30-8.40 (1H, m), 8.43-8.65 (1H, m), 10.88 (1H, brs).

ESI-MS (m/e): 406 (M+H).

**Example 8**5-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-hydroxy-benzoic acid dimethyl amide, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.00 (3H, brs), 3.08 (3H, brs), 6.83 (1H, d, J = 8.8 Hz), 6.86 (1H, d, J = 8.8 Hz), 7.18-7.23 (2H, m), 7.26-7.36 (3H, m), 7.38-7.42 (1H, in), 7.61 (1H, d, J = 2.5 Hz), 7.89 (1H, dd, J = 7.7, 7.7 Hz), 8.19-8.38 (2H, m), 8.36 (1H, d, J = 7.7 Hz), 8.63 (1H, d, J = 4.8 Hz)

ESI-MS (m/e): 452 (M+H).

**Example 9****5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 4-methanesulphonyl-phenol, the title compound was obtained by the same method as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.40 (3H, s), 6.96 (2H, d, J = 8.8 Hz), 7.10-7.16 (1H, m), 7.17-7.25 (1H, m), 7.32 (1/2H, s), 7.38, (1/2H, s), 7.39-7.43 (1H, m), 7.65 (1/2H, s), 7.70 (1/2H, s), 7.83 (2H, dd, J = 8.8, 3.1 Hz), 7.90 (1H, ddd, J = 7.8, 7.8, 1.7 Hz), 8.23 (1H, brs), 8.32 (1H, brs), 8.39 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 4.7 Hz), 10.84 (1H, brs).

ESI-MS (m/e): 459 (M+H).

**Example 10****5-(4-methoxycarbonyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 4-hydroxy-benzoic acid methyl ester, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.88 (3H, s), 6.82 (2H, d, J = 8.8 Hz), 7.12 (1H, ddd, J = 8.6, 2.9, 1.5 Hz), 7.18 (1H, dd, J = 8.6, 4.8 Hz), 7.28 (1H, brs), 7.32 (1H, brs), 7.87 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 7.92 (2H, d, J = 8-8 Hz), 8.20 (1H, d, J = 2.9 Hz), 8.27 (1H, d, J = 4.8 Hz), 8.37 (1H, dd, J = 7.7, 1.1 Hz), 8.61 (1H, dd, J = 5.1, 1.8 Hz), 10.80 (1H, brs)

ESI-MS (m/e): 439 (M+H).

**Example 11****5-(2-formyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 2-hydroxy-benzaldehyde, the title compound was obtained as a straw-coloured solid by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.80 (1H, d, J = 8.4 Hz), 6.92-7.58 (6H, m), 7.83 (1H, d, J = 8.0 Hz), 7.87 (1H, td, J = 7.6 Hz, 1.2 Hz), 8.12-8.34 (3H, m), 8.39 (1H, d, J = 8.4 Hz), 8.55-8.67 (1H, m), 10.06 (1H, s)

ESI-MS (m/e): 409 (M+H).

**Example 12****5-(2-carboxy-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 2-hydroxybenzoic acid, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 6.83 (2H, d, J = 8.8 Hz), 7.31 (1H, ddd, J = 8.6, 2.9, 1.5 Hz), 7.34 (1H, ddd, J = 8.6, 4.8, 0.7 Hz), 7.48 (1H, dd, J = 7.7, 4.8 Hz), 7.54 (1H, s), 7.56 (1H, s), 7.92 (2H, d, J = 8.8 Hz), 7.96 (1H, ddd, J = 7.7, 7.7, 1.5 Hz), 8.9 (1H, dd, J = 2.9, 0.7 Hz), 8.20 (1H, dd, J = 4.8,

1.5 Hz), 8.27 (1H, d, J = 7.7 Hz), 8.72 (1H, d, J = 4.8 Hz).

ESI-MS (m/e): 425 (M+H).

#### Example 13

##### 5-(2-methyl-pyridin-5-yl sulphanyl)-2-pyridine-2-yl- 6-(pyridine-3- yloxy)-1H- benzimidazole

Using 6-methyl-pyridine-3-thiol, the title compound was obtained by the same process as in Example 2, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.53 (3H, s), 7.05 (1H, d, J = 7.6 Hz), 7.05, 7.36 (tautomer, 1H, s), 7.12-7.24 (2H, m), 7.32-7.36 (1H, m), 7.44, 7.76 (tautomer, 1H, s), 7.50-7.56 (1H, m), 7.83 (1H, t, J = 8.0 Hz), 8.26-8.36 (3H, m), 8.45 (1H, s), 8.56 (1H, d, J = 4.4 Hz), 11.28-11.40, 11.40-11.50 (tautomer, 1H, brs).

ESI-MS (m/e): 412 (M+H).

#### Example 14

##### 5-(2-ethoxycarbonyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

4-methanesulphonyl-phenol and 2-hydroxybenzoic acid ethyl ester were successively used, and, by the same process as in Example 1, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.19 (3H, t, J = 7.0 Hz), 3.03 (3H, s), 4.14 (2H, q, J = 7.0 Hz), 6.87 (1H, dd, J = 7.4, 6.3 Hz), 7.00 (2H, dd, J = 9.0, 2.2 Hz), 7.10-7.17 (1H, m), 7.14 (1/2H, brs), 7.32 (1/2H, brs), 7.37-7.43 (2H, m), 7.49 (1/2H, brs), 7.67 (1/2H, brs), 7.81 (2H, dd, J = 9.0, 2.2 Hz), 7.82-7.90 (2H, m), 8.36-8.40 (1H, m), 8.62-8.64 (1H, m), 10.85 (1H, brs).

ESI-MS (m/e): 530 (M+H).

#### Example 15

##### 5-(2-dimethylcarbamoyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

4-fluoro-5-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 2-hydroxybenzoic acid dimethyl amide were successively used, and, by the same process as in Example 14, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.58-3.06 (9H, m), 6.83 (1/3H, d, J = 8.6 Hz), 6.86 (2/3H, d, J = 8.4 Hz), 7.02-7.11 (3H, m), 7.12-7.18 (2H, m), 7.12-7.18 (1/2H, m), 7.23-7.33 (1H, m), 7.23-7.33 (1/2H, m), 7.36-7.40 (1H, m), 7.58 (1/3H, s), 7.64 (2/3H, s), 7.83-7.90 (3H, m), 8.34-8.38 (1H, m), 8.62-8.64 (1H, m), 10.58 (2/3H, brs), 10.61 (1/3H, brs)

ESI-MS (m/e): 529 (M+H).

**Example 16**5-(2-methoxy-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-methoxy-phenol, the title compound was obtained by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.03 (3H, s), 3.69 (3H, s), 6.87-6.95 (3H, m), 7.00 (1/2H, s), 7.08 (2H, dd, J = 8.9, 2.8 Hz), 7.08-7.38 (1H, m), 7.31 (1/2H, s), 7.35 (1/2H, s), 7.35-7.38 (1H, m), 7.64 (1/2H, s), 7.83 (2H, dd, J = 8.9, 2.8 Hz), 7.87 (1H, dd, J = 7.8, 1.6 Hz), 8.33-8.38 (1H, m), 8.60-8.62 (1H, m), 10.62 (1/2H, brs), 10.73 (1/2H, brs).

ESI-MS (m/e): 488 (M+H).

**Example 17**5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 2-hydroxy-benzonitrile, the title compound was obtained as a colourless solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.78 (1H, d, J = 8.4 Hz), 6.86 (2H, t, J = 9.6 Hz), 7.09 (1H, dd, J = 8.4 Hz, 12.8 Hz), 7.37-7.55 (4H, m), 7.62-7.92 (4H, m), 8.40 (1H, d, J = 8.4 Hz), 8.64 (1H, d, J = 4.0 Hz).

ESI-MS (m/e): 483 (M+H).

**Example 18**5-(4-dimethylcarbamoyl-phenoxy)-6-phenoxy-2-pyridine-2-yl-1H-benzimidazole

4-hydroxybenzoic acid dimethyl amide and phenol were successively used, and, by the same process as in Example 1, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.99 (3H, brs), 3.07 (3H, brs), 6.85-6.88 (4H, m), 6.97-7.14 (1H, m), 7.21-7.27 (3H, m), 7.31-7.37 (3H, m), 7.55 (1/2H, brs), 7.61 (1/2H, brs), 7.84 (1H, ddd, J = 7.7, 7.7, 1.5 Hz), 8.35 (1H, d, J = 7.7 Hz), 8.61 (1H, brs), 10.48 (1/2H, brs), 10.51 (1/2H, brs).

ESI-MS (m/e): 451 (M+H).

**Example 19**5-(4-dimethylcarbamoyl-phenoxy)-6-(4-methyl sulfanyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-fluoro-5-(4-dimethylcarbamoyl-phenoxy)-2-nitro-phenylamine obtained in Example 18 and 4-methylmercapto-phenol, the title compound was obtained by the same process as in Example 1, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.44 (3H, s), 2.99 (3H, brs), 3.07 (3H, brs), 6.81 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 7.18 (2H, d).

ESI-MS (m/e): 497 (M+H).

#### Example 20

5-(4-dimethylcarbamoyl-phenoxy)-6-(2-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-methanesulphonyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.94 (3/2H, s), 2.99 (3H, brs), 3.03 (3/2H, brs), 3.08 (3H, brs), 6.88-6.93 (3H, m), 7.15-7.22 (1H, m), 7.24 (1/2H, s), 7.34-7.42 (3H, m), 7.39 (1/2H, s), 7.45-7.52 (1H, m), 7.64 (1/2H, s), 7.70 (1/2H, s), 7.86-7.90 (1H, m), 8.00 (1H, d, J = 7.8 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 3.9 Hz), 10.72 (1H, brs).

ESI-MS (m/e): 529 (M+H).

#### Example 21

5-(4-dimethylcarbamoyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-methanesulphonyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.00 (3H, brs), 3.03 (3H, s), 3.08 (3H, brs), 6.81 (2H, d, J = 8.1 Hz), 6.95 (2H, d, J = 8.4 Hz), 7.26 (1/2H, brs), 7.32 (2H, d, J = 8.1 Hz), 7.39 (1H, dd, J = 7.7, 4.9 Hz), 7.64 (1/2H, brs), 7.66 (1/2H, brs), 7.79 (2H, d, J = 8.4 Hz), 7.87 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 8.37 (1H, d, J = 7.7 Hz), 8.63 (1H, d, J = 4.9 Hz), 10.77 (1H, brs).

ESI-MS (m/e): 529 (M+H).

#### Example 22

5-(4-dimethylcarbamoyl-phenoxy)-6-(4-methoxy-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-methoxy-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.00-3.07 (6H, m), 3.76 (3/2H, s), 3.77 (3/2H, s), 6.74-6.86 (4H, m), 6.91 (2H, d, J = 8.4 Hz), 7.05 (1/2H, brs), 7.19 (1/2H, brs), 7.32-7.36 (1H, m), 7.35 (2H, d, J = 8.4 Hz), 7.43 (1/2H, brs), 7.58 (1/2H, brs), 7.83 (1H, dd, J = 7.7, 7.7 Hz), 8.33 (1H, dd, J = 7.7, 3.17 Hz), 8.58-8.61 (1H, m), 10.58 (1/2H, brs), 10.79 (1/2H, brs).

ESI-MS (m/e): 481 (M+H).

#### Example 23

5-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-2-yloxy)-1H-benzimidazole ditrifluoroacetic acid salt

Using 2-hydroxypyridine, the title compound was obtained as yellow solid by the same process

as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 6.93-7.13 (4H, m), 7.37-7.45 (2H, m), 7.41 (1Hx1/2, s), 7.56 (1Hx1/2, s), 7.64 (1Hx1/2, s), 7.67-7.75 (1H, m), 7.77-7.84 (1H, m), 7.81 (1Hx1/2, s), 8.02-8.06 (1H, m), 8.12-8.20 (1H, m), 8.27-8.33 (1H, m), 8.82-8.87 (1H, m).

ESI-MS (m/e): 452 (M+H).

#### Example 24

##### 5-(4-dimethylcarbamoyl-phenoxy)-6-(2-ethoxycarbonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-hydroxybenzoic acid ethyl ester, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.20 (3H, t, J = 7.0 Hz), 3.01 (3H, brs), 3.07 (3H, brs), 4.17 (2H, q, J = 7.0 Hz), 6.80-6.91 (3H, m), 7.08-7.14 (1H, m), 7.12 (1/2H, brs), 7.18 (1/2H, brs), 7.26-7.41 (4H, m), 7.49 (1/2H, brs), 7.61 (1/2H, brs), 7.84-7.87 (2H, m), 8.34-8.38 (1H, m), 8.61-8.62 (1H, m), 10.85 (1/2H, brs), 10.95 (1/2H, brs).

ESI-MS (m/e): 523 (M+H).

#### Example 25

##### 5-(2-dimethylcarbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-hydroxybenzoic acid dimethyl amide, the title compound was obtained as straw-coloured solid by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 2.64-3.08 (12H, m), 6.81 (1/2H, s), 6.85 (1/2H, s), 6.94 (1H, dd, J = 8.8, 2.7 Hz), 7.08 (1/2H, s), 7.12 (1/2H, s), 7.21 (1/2H, s), 7.24 (1/2H, s), 7.25-7.29 (2H, m), 7.30-7.34 (1H, m), 7.35-7.53 (2H, m), 7.59 (1H, d, J = 3.1 Hz), 7.83-7.88 (1H, m), 8.33-8.38 (1H, m), 8.63 (1H, d, J = 4.9 Hz), 10.52 (1H, brs)

ESI-MS (m/e): 522 (M+H).

#### Example 26

##### 5-(2-acetyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 2-acetyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 2.36 (3/2H, s), 2.40 (3/2H, s), 3.00 (3H, brs), 3.08 (3H, brs), 6.76-6.84 (3H, m), 7.05-7.11 (1H, m), 7.15-7.25 (1H, m), 7.26-7.28 (1H, m), 7.32-7.35 (2H, m), 7.38-7.42 (1H, m), 7.63 (1/2H, s), 7.68 (1/2H, s), 7.78 (1H, d, J = 7.4 Hz), 7.86-7.90 (1H, m), 8.39 (1H, d, J = 7.0 Hz), 8.65 (1H, s), 10.73 (1Hx1/2, brs), 10.88 (1Hx1/2, brs).

ESI-MS (m/e): 493 (M+H).



**Example 27****5-(4-acetyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole**

Using 4-acetyl-phenol, the title compound was obtained by the same process as in Example 19, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.55 (3H, s), 2.98 (3H, brs), 3.09 (3H, brs), 6.70-6.90 (4H, m), 7.23 (1/2H, s), 7.34 (1/2H, s), 7.26 (1/2H, s), 7.33-7.35 (2H, m), 7.38-7.42 (1H, m), 7.65 (1/2H, s), 7.68 (1/2H, s), 7.86-7.91 (3H, m), 8.40 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 3.5 Hz), 10.85 (1/2H, brs), 10.95 (1/2H, brs).

ESI-MS (m/e): 493 (M+H).

**Example 28****5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-cyano-phenoxy)-1H-benzimidazole**

2-hydroxy-benzonitrile and 4-hydroxy-benzonitrile were successively used, and the title compound was obtained as a colourless solid by the same method as in Example 1, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.80 (1H, t, J = 8.8 Hz), 6.86 (1H, d, J = 8.8 Hz), 6.89 (1H, d, J = 8.8 Hz), 7.08 (1H, td, J = 7.6 Hz, 7.4 Hz), 7.34-7.47 (3H, m), 7.47-7.58 (3H, m), 7.67 (1H, d, J = 5.2 Hz), 7.88 (1H, t, J = 7.6 Hz), 8.38 (1H, d, J = 7.6 Hz), 8.65 (1H, d, J = 4.0 Hz), 10.58 (1H, brs)

ESI-MS (m/e): 430 (M+H).

**Example 29****5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(3-cyano-phenoxy)-1H-benzimidazole**

Using 4-fluoro-5-(2-cyano-phenoxy)-2-nitro-phenylamine obtained in Example 28 and 3-hydroxy-benzonitrile, the title compound was obtained as a brown solid by the same process as in Example 28, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.93-6.84 (1H, m), 6.96-7.12 (3H, m), 7.27-7.38 (3H, m), 7.38-7.48 (2H, m), 7.54 (1H, dd, J = 1.6 Hz, 7.6 Hz), 7.68 (1H, d, J = 13.2 Hz), 7.89 (1H, t, J = 7.6 Hz), 8.42 (1H, d, J = 7.6 Hz), 8.65 (1H, s).

ESI-MS (m/e): 430 (M+H).

**Example 30****5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-(2-hydroxyethyl)-phenoxy)-1H-benzimidazole  
monotrifluoroacetic acid salt**

Using 4-hydroxyethyl-phenol, the title compound was obtained as a brown solid by the same process as in Example 29, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 2.78 (2H, t, J = 7.0 Hz), 3.72 (2H, t, J = 7.0 Hz), 6.83 (2H, d, J = 8.6 Hz),

6.94 (1H, d, J = 8.6 Hz), 7.19-7.21 (3H, m), 7.41 (1H, s), 7.56 (1H, t, J = 8.6 Hz), 7.63-7.73 (3H, m), 8.11 (1H, t, J = 7.8 Hz), 8.26 (1H, d, J = 7.8 Hz), 8.85 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 449 (M+H).

### Example 31

#### 5-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(1-oxy-pyridine-3-yloxy)-1H-benzimidazole

1-oxy-pyridin-3-ol and 4-cyano-phenol were successively used, and, by the same process as in Example 1, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.86-6.90 (2H, m), 7.11 (1/2H, ddd, J = 7.3, 2.8, 1.5 Hz), 7.13 (1/2H, ddd, J = 7.3, 2.8, 1.5 Hz), 7.18 (1/2H, dd, J = 7.3, 4.8 Hz), 7.20 (1/2H, dd, J = 7.3, 4.8 Hz), 7.36-7.41 (1H, m), 7.37 (1/2H, s), 7.44 (1/2H, s), 7.48-7.57 (3H, m), 7.60 (1/2H, s), 7.66 (1/2H, s), 8.20 (1/2H, d, J = 2.8 Hz), 8.21 (1/2H, d, J = 2.8 Hz), 8.30 (1/2H, dd, J = 4.8, 1.5 Hz), 8.32 (1/2H, dd, J = 4.8, 1.5 Hz), 8.37 (1H, d, J = 7.0 Hz), 8.65-8.70 (1H, m).

ESI-MS (m/e): 422 (M+H).

### Example 32

#### Production of 2-pyrazine-2-yl-5,6-bis(pyridine-3-yloxy)-1H-benzimidazole

To pyridine 1 ml solution of 4,5-bis-(pyridine-3-yloxy)-benzene-1,2-diamine 15 mg obtained in Example 1 (Step 3) were added pyrazine-2-carboxylic acid 7.7 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 20 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was suspended in phosphorus oxychloride 1 ml, and the reaction liquor was stirred at 100°C overnight. Phosphorus oxychloride was eliminated by distillation under reduced pressure and thereafter, it was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution and thereafter, dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol=15/1+0.1 % ammonia water), and obtained the title compound as yellow solid.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ : 7.20-7.82 (6H, m), 8.11 (2H, s), 8.20-8.28 (2H, m), 8.67 (1H, s), 8.75 (1H, s), 9.47 (1H, s)

ESI-MS (m/e): 383 (M+H).

### Example 33

5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-(4-methanesulphonyl-phenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 9, the title compound was obtained by the same process as in Example 32, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.91 (3H, s), 3.04 (3H, d, J = 1.6 Hz), 6.96 (2H, d, J = 9.0 Hz), 7.14-7.18 (1H, m), 7.19-7.25 (1H, m), 7.35 (1/2H, s), 7.41 (1/2H, s), 7.68 (1/2H, s), 7.73 (1/2H, s), 7.84 (2H, dd, J = 9.0, 1.6 Hz), 8.24 (1H, dd, J = 7.1, 2.7 Hz), 8.32-8.35 (1H, m), 8.59-8.62 (1H, m), 8.69 (1H, d, J = 2.5 Hz), 9.63-9.64 (1H, m), 10.91 (1Hx1/2, brs), 10.8 (1Hx1/2, brs).

ESI-MS (m/e): 460 (M+H).

**Example 34**5-(4-dimethylcarbamoyl-phenoxy)-6-(2-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(4-dimethylcarbamoyl-phenoxy)-5-(2-methanesulphonyl -phenoxy)- benzene-1,2-diamine obtained in Example 20, the title compound was obtained by the same process as in Example 32, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.95 (3/2H, s), 2.99 (3H, brs), 3.05 (3/2H, brs), 3.08 (3H, brs), 6.80-6.91 (3H, m), 6.89-6.95 (3H, s), 7.17-7.24 (1H, m), 7.20 (1/2H, s), 7.35-7.39 (2H, m), 7.35-7.39 (1/2H, m), 7.46-7.54 (1H, m), 7.66 (1/2H, s), 7.70 (1/2H, s), 8.02 (1H, d, J = 7.8 Hz), 8.60 (1H, d, J = 2.4 Hz), 8.67 (1H, dd, J = 2.4, 2.0 Hz), 9.61 (1H, d, J = 2.0 Hz), 10.65 (1/2H, brs), 10.74 (1/2H, brs).

ESI-MS (m/e): 530 (M+H).

**Example 35**5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 4-(2-cyano-phenoxy)-5-(4-methanesulphonyl-phenoxy)-benzene-1,2-diamine obtained in Example 17, the title compound was obtained as a brown solid by the same process as in Example 32, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ : 3.09 (3H, s), 6.91 (1H, d, J = 7.8 Hz), 6.96-7.00 (2H, m), 7.15 (1H, td, J = 7.6Hz, 1.0 Hz), 7.54-7.58 (1H, m), 7.64 (1H, dd, J = 1.6Hz, 7.8 Hz), 7.72 (2H, d, J = 3.5 Hz), 7.87 (2H, d, J = 8.6 Hz), 8.77 (1H, d, J = 2.7 Hz), 8.81-8.85 (1H, dd, J = 1.6Hz, 2.7 Hz), 8.52 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 484 (M+H).

**Example 36**5-(2-methoxy-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-methoxy-phenoxy)-5-(4-methanesulphonyl-phenoxy)-benzene-1,2-diamine obtained in Example 16, the title compound was obtained by the same process as in Example 32, a process

based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.04 (3H, s), 3.71 (3H, d, J = 3.1 Hz), 6.86-6.97 (3H, m), 7.00 (1/2H, s), 7.06-7.14 (3H, m), 7.34 (1/2H, s), 7.36 (1/2H, s), 7.68 (1/2H, s), 7.85 (2H, dd, J = 9.0, 3.1 Hz), 8.56-8.59 (1H, m), 8.65 (1H, dd, J = 4.3, 2.7 Hz), 9.57-9.61 (1H, m), 10.24 (1Hx1/2, brs), 10.34 (1Hx1/2, brs).

ESI-MS (m/e): 489 (M+H).

#### Example 37

##### 5-(4-dimethylcarbamoyl-phenoxy)-6-(2-methanesulphonyl-phenoxy)-2-thiazol-2-yl-1H-benzimidazole

Using thiazole-2-carboxaldehyde and 4-(4-dimethylcarbamoyl-phenoxy)-5-(2-methanesulphonyl-phenoxy)-benzene-1,2-diamine obtained in Example 20, the title compound was obtained by the same process as in Example 1 (Step 4), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 2.94 (3/2H, s), 2.96 (3H, brs), 3.05 (3/2H, brs), 3.08 (3H, brs), 6.87-6.93 (3H, m), 7.13 (1/2H, brs), 7.16-7.23 (1H, m), 7.34-7.38 (2H, m), 7.45-7.53 (1H, m), 7.51 (1/2H, brs), 7.54-7.56 (1H, m), 7.62 (1/2H, s), 7.66 (1/2H, s), 7.94 (1H, d, J = 3.1 Hz), 8.01 (1H, dd, J = 7.8, 1.6 Hz).

ESI-MS (m/e): 535 (M+H).

#### Example 38

##### 5-(2-cyano-phenoxy)-2-pyridazine-3-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

To N-methylpyrrolidone 0.3 ml solution of 4-(2-cyano-phenoxy)-5-(4-methanesulphonyl-phenoxy)-benzene-1,2-diamine 15 mg obtained in Example 17 were added successively pyridazine-3-carboxylic acid 3.3 mg, 1-hydroxybenzotriazole 15 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 15 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained residue was dissolved in N-methylpyrrolidone 0.2 ml, and trifluoromethanesulfonic acid triytterbium salt 5 mg was added, and the reaction liquor was stirred at 140°C overnight. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid]. By eliminating the solvent of the obtained fraction under reduced pressure, the title compound was obtained as a brown solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.10 (3H, s), 6.92 (1H, d, J = 7.6 Hz), 6.99 (2H, d, J = 8.6 Hz), 7.20 (1H, t, J = 7.6 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.64 (1H, d, J = 7.6 Hz), 7.70-7.80 (2H, m), 7.87 (2H, d, J = 8.6 Hz), 7.96-8.02 (1H, m), 8.58 (1H, brs), 9.36 (1H, brs).

ESI-MS (m/e): 484 (M+H).

**Example 39****5-(2-cyano-phenoxy)-2-[1,2,5]-thiadiazol-3-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole**

Using [1,2,5]-thiadiazole-3-carboxylic acid, the title compound was obtained as a brown solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.09 (3H, s), 6.90 (1H, d, J = 7.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.19 (1H, t, J = 7.7 Hz), 7.56 (1H, t, J = 7.8 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.72 (1H, s), 7.73 (1H, s), 7.87 (2H, d, J = 8.6 Hz), 9.39 (1H, s).

ESI-MS (m/e): 490 (M+H).

**Example 40****5-(2-cyano-phenoxy)-2-(2H-[1,2,3]-triazol-4-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole**

Using 2H-[1,2,3]-triazole-4-carboxylic acid, the title compound was obtained as a brown solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.12 (3H, s), 6.91 (1H, d, J = 7.6 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.20 (1H, t, d, J = 7.6 Hz), 7.70 (1H, d, J = 2-7 Hz), 7.87 (2H, d, J = 8.6 Hz), 8.52 (1H, brs).

ESI-MS (m/e): 473 (M+H).

**Example 41****5-(2-cyano-phenoxy)-2-furazane-3-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole**

Using furazane-3-carboxylic acid, the title compound was obtained as a brown solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.06 (3H, s), 6.84 (1H, d, J = 7.8 Hz), 6.92 (2H, d, J = 8.6 Hz), 7.15 (1H, t, J = 7.8 Hz), 7.52 (1H, t, J = 7.8 Hz), 7.57-7.62 (2H, m), 7.82 (2H, d, J = 8.6 Hz) ESI-MS (m/e): 474 (M+H).

**Example 42****5-(2-cyano-phenoxy)-2-(4H-[1,2,4]-triazol-3-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole**

Using [1,2,4]-triazole-3-carboxylic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.07 (3H, s), 6.92 (1H, d, J = 7.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.19 (1H, t,

J = 7.8 Hz), 7.55 (1H, t, J = 7.8 Hz), 7.63 (1H, d, J = 7.8 Hz), 7.74 (2H, d, J = 6.3 Hz), 7.85 (2H, d, J = 8.6 Hz), 8.73 (1H, s).

ESI-MS (m/e): 473 (M+H).

#### Example 43

##### 5-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

An 80 % sulphuric acid solution of 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 3.5 mg obtained in Example 5 was stirred at 50°C overnight as the reaction liquor.

The reaction mixture was purified by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and, by eliminating the solvent of the obtained fraction under reduced pressure, the title compound was obtained as a colourless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 5.59 (1H, brs), 6.80 (1H, dd, J = 8.4Hz, 0.8 Hz), 7.01-7.48 (7H, m), 7.88 (1H, td, J = 8.0Hz, 2.0 Hz), 8.16 (1H, dd, J = 8.4Hz, 2.0. Hz), 8.21 (1H, s), 8.27-8.85 (1H, m), 8.38 (1H, d, J = 8.0 Hz), 8.63 (1H, d, J = 8.4 Hz).

ESI-MS (m/e): 424 (M+H).

#### Example 44

##### 5-(4-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 7, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.82 (2H, d, J = 8.8 Hz), 7.13 (1H, ddd, J = 8.4, 2.6, 1.5 Hz), 7.17 (1H, dd, J = 8.4, 4.8 Hz), 7.13-7.20 (1H, m), 7.30-7.37 (1H, m), 7.38 (1H, ddd, J = 7.7, 40.4, 1.1 Hz), 7.71 (2H, d, J = 8.8 Hz), 7.87 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 8.16 (1H, dd, J = 2.6, 0.7 Hz), 8.25 (1H, dd, J = 4.8, 1.5 Hz), 8.39 (1H, ddd, J = 7.7, 1.1, 0.7 Hz), 8.61 (1H, ddd, J = 4.4, 1.8, 0.7 Hz).

ESI-MS (m/e): 424 (M+H).

#### Example 45

##### 5-(4-carbamoyl-phenoxy)-6-(pyridine-3-yloxy)-2-thiazol-2-yl-1H-benzimidazole

Using 4-(4,5-diamino-2-(pyridine-3-yloxy)-phenoxy)-benzonitrile obtained in Example 7, the title compound was obtained by the same process as in Example 37 and Example 43, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.01 (2H, brs), 6.82-6.86 (2H, m), 7.13 (1H, ddd, J = 8.4, 2.9, 1.5 Hz), 7.18 (1H, dd, J = 8.4, 4.6 Hz), 7.29 (1/2H, s), 7.30 (1/2H, s), 7.52-7.54 (1H, m), 7.92 (2H, d, J = 8.8 Hz), 7.61 (1/2H, s), 7.64 (1/2H, s), 7.70-7.75 (2H, m), 7.92 (1H, d, J = 2.9 Hz), 8.21 (1H, d, J

= 2.9 Hz), 8.29 (1H, dd, J = 4.6, 1.5 Hz).

ESI-MS (m/e): 430 (M+H).

#### Example 46

##### 5-(4-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-cyano-phenoxy)-1H-benzimidazole obtained in Example 28, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 7.86 (2H, d, J = 8.8 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.39 (1H, t, J = 7.6 Hz), 7.45-7.74 (4H, m), 7.78 (2H, d, J = 8.8 Hz), 7.91 (1H, d, J = 7.6 Hz), 7.99 (1H, t, J = 7.6 Hz), 8.30 (1H, d, J = 7.6 Hz), 8.74 (1H, s).

ESI-MS (m/e): 466 (M+H).

#### Example 47

##### 5-(3-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole monotrifluoroacetic acid salt

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(3-cyano-phenoxy)-1H-benzimidazole obtained in Example 29, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 6.78-6.96 (1H, m), 6.96-7.08 (1H, m), 7.08-7.20 (1H, m), 7.30-7.70 (7H, m), 7.88-8.08 (2H, m), 8.29 (1H, d, J = 7.6 Hz), 8.73 (1H, s).

ESI-MS (m/e): 466 (M+H).

#### Example 48

##### 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole obtained in Example 17, the title compound was obtained as a straw-coloured solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.12 (3H, s), 6.85 (1H, d, J = 7.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.15 (1H, t, J = 7.8 Hz), 7.42 (1H, t, J = 7.8 Hz), 7.52 (1H, dd, J = 4.3 Hz, 7.0 Hz), 7.64 (2H, brs), 7.83 (2H, d, J = 8.6 Hz), 7.91 (1H, d, J = 7.8 Hz), 8.01 (1H, dd, J = 7.0 Hz, 7.8 Hz), 8.32 (1H, d, J = 7.8 Hz), 8.76 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 501 (M+H).

#### Example 49

##### 5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(4-methanesulphonyl-phenoxy)-

-1H-benzimidazole obtained in Example 35, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.05 (3H, s), 5.80 (1H, brs), 6.82 (1H, d, J = 7.8 Hz), 6.95-7.00 (3H, m), 7.17 (2H, q, J = 8.2 Hz), 7.36-7.39 (2H, m), 7.76 (1H, d, J = 7.8 Hz), 7.81-7.85 (2H, m), 8.15 (1H, d, J = 7.8 Hz), 8.63 (1H, s), 8.72 (1H, s), 9.66 (1H, s), 10.80 (1H, brs)

ESI-MS (m/e): 502 (M+H).

#### Example 50

##### 5-(4-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(1-oxy-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(4-cyano-phenoxy)-2-pyridine-2-yl-6-(1-oxy-pyridine-3-yloxy)-1H-benzimidazole obtained in Example 31, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 6.82-6.86 (2H, m), 7.15-7.26 (2H, m), 7.38-7.42 (1H, m), 7.41 (1/2H, s), 7.44 (1/2H, s), 7.54-7.58 (1H, m), 7.62 (1/2H, s), 7.65 (1/2H, s), 7.71-7.75 (2H, m), 8.12-8.16 (1H, m), 8.22-8.27 (1H, m), 8.37 (1H, d, J = 7.0 Hz), 8.64-8.67 (1H, m).

ESI-MS (m/e): 440 (M+H).

#### Example 51

##### 5-(3-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-(3-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 6, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 7.07 (1H, ddd, J = 0.8, 3.4, 10.3 Hz), 7.36 (1H, dd, J = 1.9, 3.4 Hz), 7.40 (1H, t, J = 10.3 Hz), 7.56 (1H, s), 7.57-7.62 (2H, m), 7.69 (1H, dd, J = 7.2, 10.3 Hz), 7.73 (1H, s), 7.78 (1H, ddd, J = 0.8, 3.8, 11.4 Hz), 8.16 (1H, dt, J = 3.0, 11.0 Hz), 8.29 (1H, dt, J = 0.4, 11.0 Hz), 8.37-8.41 (2H, m), 8.80 (1H, dt, J = 0.4, 3.8 Hz).

ESI-MS (m/e): 424 (M+H)+.

#### Example 52

##### 5-(2-carbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-hydroxybenzoic acid dimethyl amide and 4-fluoro-5-(2-cyano-phenoxy)-2-nitro phenylamine obtained in Example 28, the title compound was obtained by the same procedures as in Example 1 and Example 43, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 2.98 (3H, brs), 3.07 (3H, brs), 5.72 (1H, brs), 6.76-6.83 (3H, m), 6.97 (1/2H, brs), 7.09 (1/2H, dd, J = 7.7, 7.7 Hz), 7.11 (1/2H, dd, J = 7.7, 7.7 Hz), 7.14 (1/2H, s), 7.30-7.35 (3H, m), 7.37-7.40 (1H, m), 7.67 (1H, d, J = 7.7 Hz), 7.86 (1H, ddd, J = 7.7, 7.7, 1.5



Hz), 8.12 (1H, dd, J = 7.7, 1.8 Hz), 8.14 (1H, dd, J = 7.7, 1.8 Hz), 8.38 (1H, d, J = 7.7 Hz), 8.61-8.62 (1H, m), 10.99 (1H, brs).

ESI-MS (m/e): 494 (M+H).

#### Example 53

5-(2-carbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-thiazol-2-yl-1H-benzimidazole

Using 4-(2-cyano-phenoxy)-5-bis-(4-dimethylcarbamoyl-phenoxy)-benzene-1,2-diamine obtained in Example 52, the title compound was obtained by the same procedures as in Example 37 and Example 43, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.97 (3H, brs), 3.08 (3H, brs), 5.91 (1/2H, brs), 6.00 (1/2H, brs), 6.75-6.82 (3H, m), 6.93 (1/2H, brs), 7.07-7.13 (1H, m), 7.17 (1H, brs), 7.25 (1/2H, brs), 7.32 (2H, d, J = 8.8 Hz), 7.53 (1H, d, J = 2.9 Hz), 7.65 (2H, d, J = 8.8 Hz), 7.37-7.40 (1H, m), 7.65 (1H, d, J = 7.0 Hz), 7.92-7.93 (1H, m), 8.11 (1/2H, d, J = 6.6 Hz), 8.13 (1/2H, d, J = 6.6 Hz).

ESI-MS (m/e): 500 (M+H).

#### Example 54

5-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(4-(2-[2,2,2-trifluoro-acetoxy]-ethyl)-phenoxy)-1H-benzimidazole • monotrifluoroacetic acid salt

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(4-(2-hydroxyethyl)-phenoxy)-1H-benzimidazole obtained in Example 30, and, by the same method as in Example 43, a process based on these or a combination of these with a normal procedure, the reaction mixture was refined by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and the title compound was obtained as a colourless solid by eliminating the solvent of the obtained fraction by distillation under reduced pressure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 2.94 (2H, t, J = 6.7 Hz), 4.17 (2H, t, J = 6.7 Hz), 6.84 (2H, d, J = 8.6 Hz), 6.90 (1H, d, J = 8.6 Hz), 7.19 (1H, d, J = 8.6 Hz), 7.25 (1H, d, J = 8.6 Hz), 7.41 (1H, s), 7.42-7.48 (1H, m), 7.58 (1H, s), 7.61-7.66 (1H, m), 8.09 (1H, t, J = 7.8 Hz), 8.25 (1H, d, J = 7.8 Hz), 8.83 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 563 (M+H).

#### Example 55

5-(4-carbamoyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-hydroxy-benzonitrile and 4-fluoro-5-(4-dimethylcarbamoyl-phenoxy)-2-nitro-phenylamine obtained in Example 18, the title compound was obtained by the same procedures as in Example 1 and Example 43, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.97 (3H, brs), 3.08 (3H, brs), 6.80-6.86 (4H, m), 7.26-7.29 (2H, m), 7.31 (1/2H, s), 7.35 (1/2H, s), 7.38-7.41 (1H, m), 7.66-7.70 (3H, m), 7.86-7.91 (1H, m), 8.40 (1H, d, J

= 7.8 Hz), 8.65 (1H, d, J = 4.7 Hz), 10.89 (1H, brs).

ESI-MS (m/e): 494 (M+H).

#### Example 56

##### 5-(4-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

To methanol 1 ml solution of 5-(4-methoxycarbonyl-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 3.0 mg obtained in Example 10 was added 40 % methylamine methanol solution 0.05 ml, and the reaction liquor was stirred at room temperature overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol=20/1), and the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.96 (3/2H, s), 2.97 (3/2H, s), 6.80 (1H, d, J = 8.4 Hz), 7.14-7.23 (2H, m), 7.36 (1H, brs), 7.40 (1H, dd, J = 7.7, 4.7 Hz), 7.62 (1H, brs), 7.66 (2H, d, J = 8.4 Hz), 7.90 (1H, dd, J = 7.7, 7.7 Hz), 8.10 (1H, brs), 8.20 (1H, brs), 8.37 (1H, d, J = 7.7 Hz), 8.63 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 438 (M+H).

#### Example 57

##### 5-(4-methanesulphonyl-phenoxy)-6-(2-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-(2-ethoxycarbonyl-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole obtained in Example 14, the title compound was obtained by the same process as in Example 56, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.73 (3/2H, s), 2.74 (3/2H, s), 3.03 (3H, s), 6.74-6.79 (1H, m), 6.89-76.96 (2H, m), 7.01 (1/2H, brs), 7.09-7.15 (1H, m), 7.17 (1/2H, brs), 7.30 (1/2H, brs), 7.40 (1/2H, brs), 7.40-7.44 (1H, m), 7.72 (1H, s), 7.82 (2H, dd, J = 8.2, 6.7 Hz), 7.88-7.93 (1H, m), 8.1.0-8.15 (1H, m), 8.41 (1H, d, J = 6.8 Hz), 8.66 (1H, ts), 11.09 (1/2H, brs), 11.12 (1/2H, brs).

ESI-MS (m/e): 515 (M+H).

#### Example 58

##### 5-(4-dimethylcarbamoyl-phenoxy)-6-(2-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-(2-ethoxycarbonyl-phenoxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole obtained in Example 24, the title compound was obtained by the same process as in Example 56, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.77 (3H, d, J = 3.5 Hz), 2.99 (3H, brs), 3.08 (3H, brs), 6.75-6.86 (3H, m), 7.00-7.14 (1H, m), 7.15-7.27 (1/2H, m), 7.27-7.32 (2H, m), 7.27-7.32 (1/2H, m), 7.35-7.42 (2H,

m), 7.69 (1H, s), 7.87-7.91 (1H, m), 8.11-8.17 (1H, m), 8.40 (1H, d, J = 7.4 Hz), 8.66 (1H, s), 11.01 (1H, brs).

ESI-MS (m/e): 508 (M+H).

#### Example 59

##### 5-(2-methylcarbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-(2-fluoro-4-nitro-phenoxy)-pyridine obtained in Example 1 (Step 2) and 2-hydroxybenzoic acid ethyl ester, the title compound was obtained as a brown solid by the same procedures as in Example 1 and Example 56, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.70-8.80 (3H, m), 6.77 (1H, d, J = 7.6 Hz), 7.25-7.44 (7H, m), 7.67 (1H, s), 7.82 (1H, t, J = 7.6 Hz), 8.15 (1H, t, J = 7.6 Hz), 8.18-8.26 (1H, m), 8.26-8.36 (1H, m), 8.38 (1H, d, J = 7.6 Hz), 8.64 (1H, d, J = 2.4 Hz), 10.6 (1H, brs).

ESI-MS (m/e): 438 (M+H).

#### Example 60

##### 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-(2H-tetrazol-5-yl)-phenoxy)-1H-benzimidazole • monotrifluoroacetic acid salt

To dimethylformamide 1 ml solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-cyano-phenoxy)-1H-benzimidazole 30 mg obtained in Example 17, sodium azide 30 mg and magnesium chloride 32 mg were added, and the reaction liquor was stirred at 170°C for 24 hours. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.11 (3H, s), 6.75 (2H, d, J = 8.6 Hz), 6.96 (1H, d, J = 7.6 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.51 (1H, t, J = 7.6 Hz), 7.62 (2H, d, J = 8.6 Hz), 7.58-7.69 (1H, m), 7.73 (1H, s), 7.93 (1H, s), 8.13 (1H, d, J = 7.6 Hz), 8.08-8.16 (1H, m), 8.33-8.38 (1H, m), 8.84-8.88 (1H, m).

ESI-MS (m/e): 526 (M+H).

#### Example 61

##### 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-(2-(N-hydroxycarbamimidoyl)-phenoxy)-1H-benzimidazole

To ethanol 2 ml solution of 5-(4-methanesulphonyl -phenoxy)-2-pyridine-2-yl-6-(2-cyano-phenoxy)-1H-benzimidazole 25 mg obtained in Example 17, 50 % hydroxylamine aqueous solution 0.1 ml was added, and the reaction liquor was stirred at 50°C overnight. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744

(Merck Co.), chloroform/methanol=5/1), and obtained the title compound as a colourless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.06 (3H, s), 5.12 (2H, s), 6.52 (1H, s), 6.80 (1H, d, J = 7.6 Hz), 7.11 (2H, d, J = 8.6 Hz), 7.28 (1H, t, J = 7.6 Hz), 7.47 (1H, dd, J = 7.8 Hz, 4.3 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.66 (1H, s), 7.89 (2H, d, J = 8.6 Hz), 7.96 (1H, t, J = 7.8 Hz), 8.55 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 516 (M+H).

#### Example 62

##### 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-(2-oxo-4,5-dihydro-[1,2,4]-oxadiazol-3-yl)-phenoxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.25 ml solution of 5-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole 8 mg obtained in Example 61 was added 1,1'-carbonyldiimidazole 10 mg, and the reaction liquor was stirred at 70°C for four hours. The reaction mixture was refined by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and the obtained fraction was diluted with ethyl acetate, and was washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, and thereafter, was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a colourless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.12 (3H, s), 6.84 (2H, d, J = 8.6 Hz), 6.82-6.88 (1H, m), 7.19 (1H, t, J = 7.2 Hz), 7.41-7.47 (2H, m), 7.82 (2H, d, J = 8.6 Hz), 7.91-7.97 (2H, m), 8.44 (1H, d, J = 7.8 Hz), 8.69 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 542 (M+H).

#### Example 63

##### 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-[1,2,4]-oxadiazol-3-yl-phenoxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.25 ml solution of 5-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole 8 mg obtained in Example 61 was added ortho ethyl formate ester 0.5 ml, and the reaction liquor was stirred at 100°C for three hours. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and thereafter, it was purified by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol=10/1), and the obtained the title compound as yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.03 (3H, s), 6.85-6.97 (3H, m), 7.23 (1H, t, J = 7.8 Hz), 7.40-7.45 (3H, m), 7.68-7.74 (3H, m), 7.91 (1H, t, J = 7.8 Hz), 8.03 (1H, d, J = 7.8 Hz), 8.42 (1H, d, J = 7.8 Hz),

8.65-8.68 (2H, m).

ESI-MS (m/e): 526 (M+H).

#### Example 64

##### 5-(pyridine-3-yloxy)-2-pyridine-2-yl-6-(2-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 5, the reaction liquor added acetic anhydride 0.3 ml to pyridine 0.5 ml solution of 5-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 20 mg obtained by same process as in Example 61 was stirred at 60°C overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol=10/1), and obtained the title compound as straw-coloured solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.80-7.00 (1H, m), 7.00-7.30 (4H, m), 7.30-7.44 (2H, m), 7.44-7.68 (1H, m), 7.86 (1H, td, J = 7.6 Hz, 2.0 Hz), 7.97 (1H, dd, J = 2.0 Hz, 7.6 Hz), 8.38 (1H, d, J = 7.6 Hz), 8.60 (1H, d, J = 4.8 Hz).

ESI-MS (m/e): 463 (M+H).

#### Example 65

##### 5-(4-methyl-pyridine-3-sulfonyl)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

To tetrahydrofuran 1.5 ml solution of 5-(2-methyl-pyridin-5-ylsulphanyl)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole 42 mg obtained in Example 13 were added OXONE 92 mg and water 0.1 ml, and the reaction liquor was stirred at room temperature overnight. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid]. Saturated aqueous sodium bicarbonate was added to the obtained fraction and thereafter, it was extracted with chloroform and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.63 (3H, s), 7.23 (1H, s), 7.32 (1H, d, J = 7.6 Hz), 7.44-7.50 (3H, m), 7.93 (1H, t, J = 7.6 Hz), 8.09-8.14 (1H, m), 8.28 (1H, d, J = 2.8 Hz), 8.36-8.41 (2H, m), 8.60, 8.61 (tautomer, 1H, s), 8.68 (1H, d, J = 4.8 Hz), 8.93, 8.95 (tautomer, 1H, d, J = 2.0 Hz).

ESI-MS (m/e): 444 (M+H).

#### Example 66

##### 5-(4-methanesulphonyl-phenoxy)-2-(1-oxy-pyridine-2-yl)-6-(2-carbamoyl-phenoxy)-1H-benzimidazole

To chloroform 2 ml solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole 8.0 mg obtained in Example 48 was added metachloroperbenzoic acid 1.5 mg, and the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1 % trifluoroacetic acid]. By eliminating the solvent of the obtained fraction under reduced pressure, the title compound was obtained as yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.12 (3H, s), 6.87 (1H, d, J = 7.8 Hz), 7.00 (2H, d, J = 7.8 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.43 (1H, t, J = 7.8 Hz), 7.69-7.76 (2H, m), 7.84-7.86 (3H, m), 7.92 (1H, d, J = 7.8 Hz), 8.52 (1H, d, J = 7.0 Hz), 8.64 (1H, d, J = 7.8 Hz).

ESI-MS (m/e): 517 (M+H).

#### Example 67

##### 4-(2-methoxy-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

##### Step 1

##### Synthesis of 5-fluoro-3-(2-methoxyphenoxy)-2-nitroaniline

To 2-methoxyphenol 1.64 g dissolved in tetrahydrofuran 30 ml was added sodium hydride 528 mg under ice cooling, and the reaction liquor was stirred for 30 minutes at the same temperature. Successively, 1.91 g of 3,5-difluoro-2-nitroaniline synthesised using process described in Journal of Organic Chemistry, 1978, Vol. 43, issue 6, pp.1241-1243 was added, and the reaction liquor was stirred at room temperature for two days. The reaction liquor was poured into water and was dried with anhydrous magnesium sulphate after extraction with ethyl acetate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1-4/1), and the title compound was obtained as orange colored solid.

##### Step 2

##### Synthesis of 3-(2-methoxyphenoxy)-2-nitro-5-(pyridine-3-yloxy)-aniline

To 5-fluoro-3-(2-methoxyphenoxy)-2-nitroaniline 3.03 g dissolved in dimethylformamide 30 ml were added 3-hydroxypyridine 1.24 g and potassium carbonate 5.42 g, and the reaction liquor was stirred at 90°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1-1/1-1/2), and the title compound was obtained as orange colored solid.

**Step 3****Synthesis of 3-(2-methoxyphenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine**

To methanol 20 ml solution of 3-(2-methoxyphenoxy)-2-nitro-5-(pyridine-3-yloxy)-aniline 1.33 g was added 20 % palladium hydroxide-carbon catalyst 1 g, and the reaction liquor was stirred under a hydrogen atmosphere for four hours. After eliminating the catalyst by filtration, the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2-ethyl acetate), and the title compound was obtained as pale orange color oily substance.

**Step 4****Production of 4-(2-methoxy-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Pyridine-2-carboxaldehyde 0.026 ml was added to nitrobenzene 0.5 ml solution of 3-(2-methoxyphenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine 59 mg at 120°C, and the reaction liquor was stirred at the same temperature for one hour. The reaction mixture was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-acetic acid to chloroform/methanol = 20/1). Solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol=20/1), and obtained the title compound as straw-coloured solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.79 and 3.83 (total 3H, each s), 6.20-7.40 (9H, m), 7.80-7.88 (1H, m), 8.24-8.65 (4H, m), 10.68-10.94 (1H, m).

ESI-MS (m/e): 411 (M+H).

**Example 68****4-(4-fluoro-phenoxy)-2-pyrazine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole**

Using 4-fluorophenol and 3-hydroxypyridine, pyrazine-2-carboxylic acid 18.6 mg and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 57.5 mg were added to pyridine 2 ml solution of 3-(4-fluorophenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine 46.7 mg synthesised by the same process as in Example 67, and the reaction liquor was stirred overnight, and thereafter, pyridine was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, was dried with anhydrous magnesium sulphate. By eliminating the solvent under reduced pressure, mixture of amide body was obtained as a yellow oily substance. The obtained mixture of amide body was dissolved in toluene 3 ml, and p-toluenesulfonic acid monohydrate 28 mg was added, and the reaction liquor was stirred at 120°C overnight. The reaction liquor was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>,

Art5744 (Merck Co.), chloroform/methanol=20/1), and obtained the title compound as yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.35 and 6.53 (total 1H, each d, J = 2.0 Hz), 6.77-7.31 (7H, m), 8.32-8.40 (2H, m), 8.54 and 8.56 (total 1H, each d, J = 1.8 Hz), 8.61 and 8.64 (total 1H, each d, J = 2.6 Hz), 9.59 and 9.69 (total 1H, each d, J = 1.5 Hz), 10.60 (1H, brs).

ESI-MS (m/e): 400 (M+H).

#### Example 69

6-(4-methoxy-phenoxy)-4-(1-methyl-1H-imidazol-2-yl sulphanyl)-2-pyridine-2-yl-1H-benzimidazole

Using 1-methyl-1H-imidazole-2-thiol and 4-methoxyphenol successively, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.73 and 3.74 (total 3H, each s), 3.81 (3H, s), 6.31-7.39 (9H, m), 7.78-7.88 (1H, m), 8.30 and 8.41 (total 1H, each d, J = 7.8 Hz), 8.59 and 8.73 (total 1H, each d, J = 4.5 Hz).

ESI-MS (m/e): 430 (M+H).

#### Example 70

6-(4-methoxy-phenoxy)-2-pyridine-2-yl-4-(pyridin-2-yl sulphanyl)-1H-benzimidazole

Pyridine-2-thiol and 4-methoxyphenol were successively used, and the title compound was obtained as a straw-coloured solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.80 and 3.81 (total 3H, each s), 6.86-7.50 (10H, m), 7.75-7.88 (1H, m), 8.32-8.62 (3H, m).

ESI-MS (m/e): 427 (M+H).

#### Example 71

6-(3-methoxy-phenoxy)-4-(2-methoxy-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2-methoxyphenoxy)-2-nitro-5-(pyridine-3-yloxy)-aniline obtained in Example 67 (Step 2) and 3-methoxyphenol, the title compound was obtained as a white solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.75 (3H, s), 3.79 and 3.84 (total 3H, each s), 6.24-7.23 (10H, m), 7.29-7.39 (1H, m), 7.79-7.89 (1H, m), 8.37 and 8.53 (total 1H, each d, J = 7.5 Hz), 8.56-8.65 (1H, m), 10.53-10.83 (1H, m).

ESI-MS (m/e): 440 (M+H).

#### Example 72

4-(2-methoxy-phenoxy)-6-(pyridine-3-yloxy)-2-thiazol-2-yl-1H-benzimidazole



Using 3-(2-methoxyphenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 67 (Step 3) and 2-thiazole carboxaldehyde, the title compound was obtained as yellow solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.78 and 3.82 (total 3H, each s), 6.20 and 6.44 (total 1H, each s), 6.68-7.28 (7H, m), 7.43-7.53 (1H, m), 7.88-7.98 (1H, m), 8.29-8.41 (2H, m), 10.90-11.10 (1H, m).

ESI-MS (m/e): 417 (M+H).

#### Example 73

##### 4-(2-fluoro-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-fluorophenol, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 6.18-6.78 (2H, m), 6.98-7.42 (8H, m), 7.72-7.90 (1H, m), 8.22-8.66 (3H, m), 11.3 (1H, brs).

ESI-MS (m/e): 399 (M+H).

#### Example 74

##### 4-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 4-fluorophenol, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 6.39 (1H, d, J = 2.1 Hz), 6.84 (1H, d, J = 2.1 Hz), 7.17-7.25 (4H, m), 7.39 (1H, dd, J = 8.4, 4.7 Hz), 7.45 (1H, ddd, J = 8.4, 2.8, 1.5 Hz), 7.50 (1H, dd, J = 7.7, 4.9 Hz), 7.96 (1H, ddd, J = 7.7, 7.7, 1.8 Hz), 8.22 (1H, d, J = 7.7 Hz), 8.33 (1H, dd, J = 4.7, 1.5 Hz), 8.38 (1H, d, J = 2.8 Hz), 8.69 (1H, ddd, J = 4.9, 1.8, 1.1 Hz).

ESI-MS (m/e): 399 (M+H).

#### Example 75

##### 4-(3-fluoro-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-fluorophenol, the title compound was obtained as pale-brown solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 6.47-6.98 (5H, m), 7.19-7.39 (4H, m), 7.78-7.89 (1H, m), 8.29-8.48 (3H, m), 8.58 (1H, s).

ESI-MS (m/e): 399 (M+H).

#### Example 76

##### 2-pyridine-2-yl-4,6-bis (pyridine-3-yloxy)-1H-benzimidazole

Using 3-hydroxypyridine, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 7.07 (1H, d, J = 2.0 Hz), 7.30 (1H, d, J = 2.0 Hz), 7.54 (1H, ddd, J = 7.6Hz, 4.8 Hz, 1.2 Hz), 7.85-7.95 (2H, m), 7.98 (1H, td, J = 7.6Hz, 2.0 Hz), 8.10-8.40 (2H, m), 8.22 (1H, d, J = 8.8 Hz), 8.48-8.60 (2H, m), 8.66 (1H, d, J = 2 Hz), 8.70-8.82 (2H, m)

ESI-MS (m/e): 382 (M+H).

#### Example 77

##### 4-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-2-yloxy)-1H-benzimidazole

2-cyanophenol and 2-hydroxypyridine were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 6.60-7.40 (3H, m), 6.92 (1H, d, J = 8.0 Hz), 6.99 (1H, dd, J = 6.4Hz, 5.2 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.46 (1H, dd, J = 8.0Hz, 2.4 Hz), 7.58-7.70 (2H, m), 7.70-7.90 (1H, m), 8.18 (1H, dd, J = 4.8Hz, 1.2 Hz), 8.38 (1H, d, J = 8.0 Hz), 8.60 (1H, d, J = 4.0 Hz), 10.40-11.00 (1H, m).

ESI-MS (m/e): 406 (M+H).

#### Example 78

##### 4-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-cyanophenol, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 6.55 (1/2H, s), 6.69 (1/2H, s), 6.70-7.55 (8H, m), 7.58-7.72 (1H, m), 7.76-7.80 (1H, m), 8.26-8.48 (3H, m), 8.55-8.64 (1H, m), 10.8-11.4 (1H, m).

ESI-MS (m/e): 406 (M+H).

#### Example 79

##### 4-(2-methoxycarbonyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole ditrifluoroacetic acid salt

Using 2-hydroxybenzoic acid methyl ester, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.70 (3H, s), 6.38 (1H, s), 7.14 (1H, s), 7.34 (1H, d, J = 7.6 Hz), 7.39 (1H, t, J = 7.6 Hz), 7.50-7.75 (3H, m), 7.75-7.88 (1H, m), 7.99 (1H, dd, J = 7.6Hz, 1.2 Hz), 8.07 (1H, t, J = 7.6 Hz), 8.27-8.58 (3H, m), 8.72-8.88 (1H, m).

ESI-MS (m/e): 439 (M+H).

#### Example 80

##### 4-(2-acetyl-phenoxy)-2-(pyridine-2-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 2-hydroxyacetophenone, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 2.68 (3H, s), 6.58 (1H, d, J = 2.3 Hz), 7.19 (1H, dd, J = 1.2, 8.2 Hz), 7.31 (1H, dd, J = 1.2, 7.5 Hz), 7.35 (1H, dd, J = 1.0, 7.5 Hz), 7.53-7.62 (2H, m), 7.69 (1H, dd, J = 4.7, 7.8 Hz), 7.76-7.82 (1H, m), 7.87 (1H, dd, J = 1.0, 8.2 Hz), 8.10 (1H, t, J = 7.8 Hz), 8.50-8.52 (1H, m), 8.54 (1H, d, J = 2.3 Hz), 8.62 (1H, d, J = 7.0 Hz), 8.74 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 423 (M+H).

#### Example 81

##### 4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 3-hydroxy-1-methyl-1H-pyridin-2-one, the title compound was obtained as a straw-coloured solid by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.62 (3H, s), 6.02-7.40 (8H, m), 7.84 (1H, t, J = 7.2 Hz), 8.33 (1H, d, J = 4.4 Hz), 8.33-8.50 (2H, m), 8.52-8.70 (1H, m)

ESI-MS (m/e): 412 (M+H).

#### Example 82

##### 6-(4-dimethylcarbamoyl-phenoxy)-4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.03 and 3.09 (total 6H, each s), 3.60 and 3.64 (total 3H, each s), 6.08-6.15 (1H, m), 6.42 and 6.64 (total 1H, each s), 6.82-7.41 (8H, m), 7.80-7.88 (1H, m), 8.36 and 8.45 (total 1H, each d, J = 8.2 Hz), 8.59 and 8.64 (total 1H, each d, J = 4.5 Hz).

ESI-MS (m/e): 482 (M+H).

#### Example 83

##### 4-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

2-difluoromethoxy-3-hydroxypyridine and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.02 and 3.09 (total 6H, each s), 6.36 and 6.48 (total 1H, each s), 6.84-7.67 (9H, m), 7.83 and 7.88 (total 1H, each t, J = 7.8 Hz), 7.99 and 8.00 (total 1H, each d, J = 5.0 Hz), 8.40 and 8.42 (total 1H, each d, J = 8.4 Hz), 8.61 and 8.64 (total 1H, each d, J = 4.3 Hz).

ESI-MS (m/e): 518 (M+H).

**Example 84**6-(2-methyl-pyridin-5-yl sulphanyl)-2-(pyridine-2-yl)-4-(pyridine-3-yloxy)-1H-benzimidazole

3-hydroxypyridine and 6-methylpyridine-3-thiol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 2.52 (3H, s), 6.66-6.80 (1H, brs), 7.05 (1H, d, J = 8.0 Hz), 7.20-7.28 (3H, m), 7.32 (1H, m), 7.49 (1H, dd, J = 2.0 Hz, 8.0 Hz), 7.81 (1H, t, J = 7.6 Hz), 8.32-8.40 (3H, m), 8.44 (1H, d, J = 2.0 Hz), 8.52 (1H, d, J = 4.8 Hz), 11.70-12.0 (1H, brs)

ESI-MS (m/e): 412 (M+H).

**Example 85**4-(2-cyano-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H- benzimidazole

2-cyanophenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  : 3.05 (3H, s), 3.18 (3H, s), 6.62 (1H, s), 6.92-7.08 (3H, m), 7.00 (2H, d, J = 8.8 Hz), 7.10-7.20 (2H, m), 7.36-7.50 (4H, m), 7.40 (2H, d, J = 8.8 Hz), 7.63 (1H, d, J = 6.3 Hz), 7.89 (1H, t, J = 7.8 Hz), 8.44 (1H, d, J = 7.8 Hz), 8.61 (1H, d, J = 3.9 Hz).

ESI-MS (m/e): 476 (M+H).

**Example 86**4-(2-fluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H- benzimidazole

Using 2-fluorophenol and 4-hydroxy-N,N-dimethylbenzamide successively, the title compound was obtained by the same process as in Example 67, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.02 (3H, s), 3.10 (3H, s), 6.39 (1H, s), 6.92-7.00 (3H, m), 6.96 (2H, d, J = 9.0 Hz), 7.10-7.24 (4H, m), 7.36-7.42 (3H, m), 7.39 (2H, d, J = 9.0 Hz), 7.88 (1H, d, J = 7.7 Hz), 8.51 (1H, d, J = 8.0 Hz), 8.63 (1H, d, J = 7.7 Hz).

ESI-MS (m/e): 469 (M+H).

**Example 87**4-(2-fluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H- benzimidazole

2-fluorophenol and 4-(methanesulphonyl)-phenol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.08 (3H, s), 6.44 (1H, s), 7.08 (2H, d, J = 9.0 Hz), 7.18-7.57 (5H, m), 7.59 (1H, dd, J = 3.1, 8.2 Hz), 7.90 (2H, d, J = 9.0 Hz), 8.06 (1H, t, J = 7.6 Hz), 8.64 (1H, d, J = 8.2 Hz), 18.71 (1H, d, J = 7.6 Hz).

ESI-MS (m/e): 476 (M+H).

#### Example 88

4-(2-(1-hydroxy-ethyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2-(1-hydroxyethyl)-phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.48 (3H, d, J = 6.4 Hz), 3.05 (3H, s), 3.10 (3H, s), 5.26 (1H, q, J = 6.4 Hz), 6.34 (1H, s), 7.04 (2H, d, J = 9.0 Hz), 7.05-7.10 (2H, m), 7.29-7.33 (2H, m), 7.44 (2H, d, J = 9.0 Hz), 7.57 (1H, dd, J = 4.7, 7.6 Hz), 7.68 (1H, dd, J = 2.0, 7.4 Hz), 8.04 (1H, dt, J = 1.6, 7.8 Hz), 8.37 (1H, d, J = 7.8 Hz), 8.80 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 495 (M+H).

#### Example 89

4-(2-(methanesulphonyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2-(methanesulphonyl)-phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.06 (3H, s), 3.14 (3H, s), 3.49 (3H, s), 7.03 (1H, d, J = 2.0 Hz), 7.11 (2H, d, J = 8.8 Hz), 7.22 (1H, d, J = 8.0 Hz), 7.32-7.40 (2H, m), 7.42 (1H, d, J = 2.0 Hz), 7.48 (2H, d, J = 9.0 Hz), 7.57 (1H, dd, J = 4.9, 7.8 Hz), 7.63 (1H, dd, J = 1.8, 7.9 Hz), 8.00 (1H, dt, J = 1.6, 7.8 Hz), 8.14 (1H, dd, J = 1.8, 8.0 Hz), 8.52 (1H, d, J = 8.0 Hz), 8.75 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 529 (M+H).

#### Example 90

4-(2-(acetyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2-hydroxy-acetophenone and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.68 (3H, s), 3.10 (3H, s), 3.20 (3H, s), 6.67 (1H, s), 7.05 (2H, d, J = 8.2 Hz), 7.15-7.22 (2H, m), 7.35 (1H, t, J = 7.0 Hz), 7.45 (2H, d, J = 8.2 Hz), 7.55 (1H, t, J = 7.0 Hz), 7.60-7.64 (1H, m), 7.86 (1H, d, J = 7.4 Hz), 8.08-8.14 (1H, m), 8.64 (1H, d, J = 7.4 Hz), 8.75-8.77 (1H, m)

ESI-MS (m/e): 493 (M+H).

#### Example 91

4-(2-dimethylcarbamoyl-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2-hydroxy-N,N-dimethylbenzamide and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.99 (3H, s), 3.06 (6H, s), 3.17 (3H, s), 6.91-6.94 (1H, m), 7.04 (2H, d, J = 8.6 Hz), 7.06-7.10 (1H, m), 7.17 (1H, t, J = 7.4 Hz), 7.28-7.39 (4H, m), 7.42 (2H, d, J = 8.6 Hz), 7.84 (1H, t, J = 7.8 Hz), 8.41 (1H, d, J = 7.8 Hz), 8.68 (1H, d, J = 3.9 Hz).

ESI-MS (m/e): 522 (M+H).

**Example 92**

4-(2,5-difluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2,5-difluoro phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.02 (3H, s), 3.14 (3H, s), 6.52-6.55 (1H, m), 6.90-6.99 (2H, m), 7.02 (2H, d, J = 8.2 Hz), 7.10 (1H, d, J = 2.0 Hz), 7.16-7.24 (1H, m), 7.42 (2H, d, J = 8.2 Hz), 7.54-7.60 (1H, m), 8.06 (1H, dt, J = 1.6, 7.8 Hz), 8.61 (1H, d, J = 7.8 Hz), 8.72 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 487 (M+H).

**Example 93**

4-(2,4-difluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2,4-difluoro phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.00 (3H, s), 3.09 (3H, s), 6.31 (1H, s), 6.99 (1H, s), 7.02 (2H, d, J = 8.6 Hz), 7.10-7.25 (2H, m), 7.28-7.40 (1H, m), 7.43 (2H, d, J = 8.6 Hz), 7.49-7.52 (1H, m), 7.98 (1H, d, J = 7.8 Hz), 8.34 (1H, d, J = 7.9 Hz), 8.74 (1H, d, J = 3.9 Hz).

ESI-MS (m/e): 487 (M+H).

**Example 94**

4-(2,6-difluoro-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

2,6-difluoro phenol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.02 (3H, s), 3.14 (3H, s), 6.39 (1H, s), 7.00 (2H, d, J = 8.6 Hz), 7.06-7.18 (3H, m), 7.20-7.25 (1H, m), 7.41 (2H, d, J = 8.6 Hz), 7.48-7.51 (1H, m), 7.99 (1H, dt, J = 1.6, 7.8 Hz), 8.59 (1H, d, J = 8.2 Hz), 8.70 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 487 (M+H).

#### Example 95

##### 4-(2-methoxy-phenoxy)-2-(pyridine-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 4-(methanesulphonyl) phenol, the title compound was obtained by the same process as in Example 71, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.03 (3H, s), 3.79 (3H, s), 6.32 (1H, s), 6.92-6.99 (1H, m), 7.00 (1H, s), 7.06 (2H, d, J = 8.6 Hz), 7.10-7.22 (3H, m), 7.38-7.43 (1H, m), 7.83 (2H, d, J = 8.6 Hz), 7.90 (1H, t, J = 7.8 Hz), 8.50 (1H, d, J = 7.8 Hz), 8.64 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 488 (M+H).

#### Example 96

##### 6-(4-dimethylcarbamoyl-phenoxy)-4-(1-ethyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

1-ethyl-3-hydroxy-1H-pyridin-2-one and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.38 (3H, t, J = 6.8 Hz), 3.02 and 3.09 (total 6H, each s), 4.06 (2H, q, J = 6.8 Hz), 6.15 (1H, t, J = 7.0 Hz), 6.40-7.42 (9H, m), 7.78-7.86 (1H, m), 8.32-8.42 (1H, m), 8.57-8.66 (1H, m).

ESI-MS (m/e): 496 (M+H).

#### Example 97

##### 6-(6-methyl-pyridine-3-yl phenyl)-4-(4-methyl-4H-[1,2,4] triazol-3-yl sulphonyl)-2-(pyridine-2-yl)-1H-benzimidazole

4-methyl-4H-[1,2,4] triazole-3-thiol and 6-methyl-pyridine-3-thiol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.55 (3H, s), 3.71 (3H, s), 7.17 (1H, d, J = 8.0 Hz), 7.20-7.24 (1H, brs), 7.42-7.46 (1H, m), 7.59 (1H, dd, J = 2.4 Hz, 8.0 Hz), 7.66-7.68 (1H, brs), 7.91 (1H, t, J = 8.0 Hz), 8.32-8.38 (3H, m), 8.70 (1H, d, J = 4.8 Hz).

ESI-MS (m/e): 432 (M+H).

#### Example 98

##### 4-(4-fluoro-phenoxy)-2-(5-methyl-isoxazol-3-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 5-methylisoxazole-3-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 2.50 (3H, s), 6.40 (1H, s), 6.80 (1H, s), 6.82 (1H, brs), 7.14-7.24 (4H, m), 7.38 (1H, dd, J = 8.2, 4.7 Hz), 7.44 (1H, d, J = 7.7 Hz), 8.32 (1H, d, J = 4.7 Hz), 8.36 (1H, d, J = 2.5 Hz).

ESI-MS (m/e): 403 (M+H).

#### Example 99

##### 4-(4-fluoro-phenoxy)-2-(1-methyl-1H-imidazol-4-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-imidazole-4-carboxylic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 3.72 (3H, s), 6.38 (1H, d, J = 1.8 Hz), 6.81 (1H, d, J = 1.8 Hz), 7.05-7.13 (2H, m), 7.17 (2H, t, J = 8.8 Hz), 7.36-7.43 (2H, m), 7.75 (1H, s), 7.78 (1H, d, J = 1.1 Hz), 8.28 (1H, s), 8.35 (1H, d, J = 2.2 Hz).

ESI-MS (m/e): 402 (M+H).

#### Example 100

##### 4-(4-fluoro-phenoxy)-2-(3-methyl-[1,2,4]thiadiazol-5-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole • monotrifluoroacetic acid salt

Using 3-methyl [1,2,4] thiadiazole-5-carboxylic acid synthesised by a process in accordance with patent EP0726260 and by combining this process with normal method, the title compound was obtained as a brown solid by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 2.70 (3H, s), 6.44 (1H, d, J = 2.2 Hz), 6.87 (1H, s), 7.15-7.27 (4H, m), 8.39 (1H, dd, J = 4.5, 1.5 Hz), 8.44 (1H, d, J = 2.5 Hz).

ESI-MS (m/e): 420 (M+H).

#### Example 101

##### 4-(4-fluoro-phenoxy)-2-isoxazol-3-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using isoxazole-3-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 6.41 (1H, d, J = 2.4 Hz), 7.01 (1H, d, J = 2.4 Hz), 7.02-7.20 (5H, m), 7.51 (1H, dd, J = 4.4 Hz, 8.4 Hz), 7.59 (1H, dd, J = 2.4 Hz, 8.4 Hz), 8.32 (1H, d, J = 4.4 Hz), 8.35 (1H, d, J = 2.4 Hz), 8.84 (1H, d, J = 2.4 Hz).

ESI-MS (m/e): 389 (M+H).



**Example 102**4-(4-fluoro-phenoxy)-2-pyrimidine-4-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using pyrimidine-4-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.60 (3H, s), 6.98-7.40 (8H, m), 8.30-8.50 (2H, m), 8.63 (1H, s), 10.40-11.00 (1H, m).

ESI-MS (m/e): 400 (M+H).

**Example 103**4-(4-fluoro-phenoxy)-2-pyrimidine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

Using pyrimidine-2-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ : 6.42 (1H, s), 6.98 (1H, s), 7.10-7.30 (5H, m), 7.36-7.60 (2H, m), 8.22-8.42 (2H, m), 8.90-9.10 (1H, m), 9.20 (1H, s).

ESI-MS (m/e): 400 (M+H).

**Example 104**4-(4-fluoro-phenoxy)-2-(1H-imidazol-2-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 1H-imidazole-2-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 6.44 (1H, d, J = 2.0 Hz), 7.00 (1H, d, J = 2.0 Hz), 7.05-7.18 (4H, m), 7.25 (2H, s), 7.39 (1H, dd, J = 3.2Hz, 8.4 Hz), 7.42-7.50 (1H, m), 8.26 (1H, dd, J = 1.6Hz, 4.4 Hz), 8.29 (1H, d, J = 3.2 Hz).

ESI-MS (m/e): 388 (M+H).

**Example 105**4-(4-fluoro-phenoxy)-2-(1-methyl-1H-imidazol-2-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-imidazole-2-carboxylic acid, the title compound was obtained by the same process as in Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.98-4.38 (3H, m), 6.38-6.60 (1H, m), 6.60-6.80 (1H, m), 6.80-7.40 (8H, m), 8.20-8.44 (2H, m)

ESI-MS (m/e): 402 (M+H).

**Example 106**4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-2-[1,2,4] thiadiazol-5-yl-1H-benzimidazole

Using [1,2,4] thiadiazole-5-carboxylic acid synthesised by process in Reference Example 1, the title compound was obtained as a straw-coloured oily substance by the same process as in

Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD80D)  $\delta$  : 6.42 (1H, s), 6.90-7.23 (5H, m), 7.39-7.50 (2H, m), 8.25-8.32 (2H, m), 8.86 (1H, s).

ESI-MS (m/e): 406 (M+H).

#### Example 107

4-(2,6-difluoro-phenoxy)-2-(pyrazine-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H- benzimidazole  
2,6-difluoro phenol and 4-(methanesulphonyl) phenol were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.03 (3H, s), 6.28 (1H, s), 7.08 (1H, s), 7.17 (2H, d, J = 9.4 Hz), 7.19-7.24 (2H, m), 7.30-7.40 (1H, m), 7.93 (2H, d, J = 9.4 Hz), 8.70-8.75 (1H, m), 8.77-8.82 (1H, m), 9.55-9.60 (1H, m).

ESI-MS (m/e): 495 (M+H).

#### Example 108-1, 108-2

4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H- benzimidazole,  
and

4-(2-methoxy-pyridine-3-yloxy)-2- pyridine-2-yl-6-(pyridine-3-yloxy)-1H- benzimidazole  
3-hydroxy-2-methoxypyridine, 3-hydroxypyridine and picolinic acid were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was respectively obtained.

4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H- benzimidazole  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 6.10-7.35 (8H, m), 7.77-7.84 (1H, m), 8.30-8.41 (3H, m), 8.53 (1H, d, J = 4.4 Hz).

ESI-MS (m/e): 398 (M+H).

4-(2-methoxy-pyridine-3-yloxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.95 and 3.99 (total 3H, each s), 6.25 and 6.45 (total 1H, each s), 6.80-7.45 (6H, m), 7.79-7.90 (1H, m), 8.00 (1H, d, J = 1.5 Hz), 8.30-8.63 (4H, m).

ESI-MS (m/e): 412 (M+H).

#### Example 109-1, 109-2

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-methoxy-pyridine-3-yloxy)-2-pyridine-2-yl-1H-  
benzimidazole and

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-  
enzimidazole

3-hydroxy-2-methoxypyridine, 4-hydroxy-N,N-dimethylbenzamide and picolinic acid were successively used, and the title compound was respectively obtained by the same method as in Examples 108-1, 108-2, a process based on this or a combination of these with a normal procedure.

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-methoxy-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.03 and 3.08 (total 6H, each s), 3.95 and 4.00 (total 3H, each s), 6.27 and 6.47 (total 1H, each d, J = 1.8 Hz), 6.80-7.45 (8H, m), 7.80-7.91 (1H, m), 7.98-8.03 (1H, m), 8.38 and 8.48 (total 1H, each d, J = 7.8 Hz), 8.61 and 8.64 (total 1H, each d, J = 4.8 Hz)

ESI-MS (m/e): 482 (M+H).

6-(4-dimethylcarbamoyl-phenoxy)-4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.03 and 3.08 (total 6H, each s), 6.18 and 6.23 (total 1H, each t, J = 7.0 Hz), 6.52 and 6.73 (total 1H, each d, J = 1.8 Hz), 6.80-7.42 (8H, m), 7.79 and 7.84 (total 1H, each t, J = 7.8 Hz), 8.37 and 8.40 (total 1H, each d, J = 7.8 Hz), 8.56 and 8.57 (total 1H, each d, J = 5.0 Hz).

ESI-MS (m/e): 468 (M+H).

**Example 110**

4-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole  
ditrifluoroacetic acid salt

Using 4-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(pyridine-3-yloxy)-1H-benzimidazole obtained in Example 78, and, by the same process as in Example 43, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 6.61 (1H, d, J = 2.0 Hz), 7.19 (1H, d, J = 8.0 Hz), 7.22 (1H, s), 7.31 (1H, td, J = 7.6Hz, 1.2 Hz), 7.48-7.60 (2H, m), 7.72-7.80 (1H, m), 7.83 (1H, dd, J = 7.6Hz, 1.2 Hz), 7.87-7.95 (1H, m), 8.03 (1H, td, J = 8.0Hz, 1.2 Hz), 8.01 (1H, dd, J = 7.6Hz, 1.2 Hz), 8.45 (1H, d, J = 5.2 Hz), 8.48-8.54 (1H, m), 8.76-8.84 (1H, m).

ESI-MS (m/e): 424 (M+H).

**Example 111**

4-(2-carbamoyl-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-cyano-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole obtained in Example 85, the title compound was obtained by the same process as in Example 110,

a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 2.99 (3H, s), 3.08 (3H, s), 6.56 (1H, s), 6.86-6.92 (1H, m), 6.95 (2H, J = 8.9 Hz), 7.04-7.08 (2H, m), 7.30-7.38 (4H, m), 7.36 (2H, d, J = 8.9 Hz), 7.52 (1H, d, J = 7.6 Hz), 7.80 (1H, t, J = 7.9 Hz), 8.36 (1H, d, J = 7.9 Hz), 8.52 (1H, d, J = 3.7 Hz).

ESI-MS (m/e): 494 (M+H).

#### Example 112

4-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-cyano-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole obtained in Example 85, the title compound was obtained by the same process as in Example 61, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.02 (3H, s), 3.16 (3H, s), 6.61 (1H, d, J = 2.0 Hz), 6.95 (1H, d, J = 2.0 Hz), 6.97 (2H, d, J = 8.6 Hz), 7.14-7.22 (2H, m), 7.38 (2H, d, J = 8.6 Hz), 7.52 (1H, dd, J = 4.9, 7.6 Hz), 7.56-7.62 (1H, m), 7.63-7.67 (1H, m), 7.97 (1H, dt, J = 1.6, 7.8 Hz), 8.48 (1H, d, J = 7.8 Hz), 8.68 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 509 (M+H).

#### Example 113

4-(2-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole obtained in Example 112, the title compound was obtained by the same process as in Example 64, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 2.70 (3H, s), 3.02 (3H, s), 3.15 (3H, s), 6.91 (1H, s), 7.04 (2H, d, J = 8.6 Hz), 7.30-7.38 (3H, m), 7.44 (2H, d, J = 8.6 Hz), 7.50-7.58 (2H, m), 7.95 (1H, d, J = 7.8 Hz), 8.02 (1H, t, J = 7.8 Hz), 8.63 (1H, d, J = 8.6 Hz), 8.71 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 533 (M+H).

#### Example 114

4-(2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-1H-benzimidazole

Using

4-(2-(N-hydroxycarbamimidoyl)-phenoxy)-2-(pyridine-2-yl)-6-(4-dimethylcarbamoyl-phenoxy)-

1H-benzimidazole obtained in Example 112, the title compound was obtained by the same process as in Example 62, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.04 (3H, s), 3.15 (3H, s), 6.74 (1H, s), 6.99 (2H, d, J = 8.6 Hz), 7.10 (1H, s), 7.28-7.36 (2H, m), 7.44 (2H, d, J = 8.6 Hz), 7.50-7.58 (2H, m), 7.89 (1H, d, J = 7.8 Hz), 8.00-8.07 (1H, m), 8.56-8.64 (2H, m).

ESI-MS (m/e): 535 (M+H).

### Example 115

#### 4-(4-fluoro-phenoxy)-2-(pyrazol-1-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

##### Step 1

##### Synthesis of 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazole-2-thiol

Carbon disulfide 0.06 ml and potassium hydroxide 54 mg were added to ethanol 2.0 ml solution of 3-(4-fluoro-phenoxy)-5-(pyridine-3-yloxy)-benzene-1,2-diamine 273 mg obtained in Example 68, and the reaction liquor was stirred at 80°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

##### Step 2

##### Synthesis of (4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazol-2-yl)-hydrazine

Hydrazine monohydrate 1.0 ml was added to 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazole-2-thiol 130 mg, and the reaction liquor was stirred at 130°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™<sub>60F<sub>254</sub></sub>, Art5744 (Merck Co.), hexane/ethyl acetate=1/1), and obtained the title compound.

##### Step 3

##### Production of 4-(4-fluoro-phenoxy)-2-(pyrazol-1-yl)-6-(pyridine-3-yloxy)-1H-benzimidazole

To ethanol 0.3 ml solution of (4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazol-2-yl)-hydrazine 8.3 mg was added tetramethoxy propane 0.012 ml, and the reaction liquor was stirred at 80°C overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™<sub>60F<sub>254</sub></sub>, Art5744 (Merck Co.), chloroform/methanol=9/1), and obtained the title compound.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 6.36 (1H, d, J = 2.6 Hz), 6.48-6.51 (2H, m), 6.77 (1H, d, J = 2.6 Hz), 7.05 (2H, d, J = 6.9 Hz), 7.11-7.18 (1H, m), 7.22-7.28 (2H, m), 7.72-7.75 (1H, m), 8.80-8.38 (2H, m), 8.48 (1H, d, J = 3.8 Hz).

ESI-MS (m/e): 388 (M+H).

#### Example 116

##### 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-2-[1,2,4] triazol-1-yl-1H-benzimidazole

###### Step 1

###### Synthesis of 4-(4-fluoro-phenoxy)-2-methyl sulphanyl-6-(pyridine-3-yloxy)-1H- benzimidazole

To dimethylformamide 1.0 ml solution of 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy)-1H-benzimidazole-2-thiol 78 mg synthesised in Example 115, potassium carbonate 30 mg and methyl iodide 0.014 ml were added, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

###### Step 2

###### Synthesis of 4-(4-fluoro-phenoxy)-2-methanesulphonyl-6-(pyridine-3-yloxy)-1H- benzimidazole

To chloroform 1.0 ml solution of 4-(4-fluoro-phenoxy)-2-methyl sulphanyl-6-(pyridine-3-yloxy)-1H-benzimidazole 80 mg was added metachloro perbenzoic acid 84 mg, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), ethyl acetate), and obtained the title compound.

###### Step 3

###### Production of 4-(4-fluoro-phenoxy)-6-(pyridine-3-yloxy) -2-[1,2,4] triazol-1-yl-1H-benzimidazole

To dimethylformamide 0.5 ml solution of 4-(4-fluoro-phenoxy)-2-methanesulphonyl-6-(pyridine-3-yloxy)-1H-benzimidazole 16 mg was added sodium hydride 5.0 mg, and thereafter, [1,2,4]-triazole 10.4 mg was added, and the reaction liquor was stirred at 160°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer

chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), ethyl acetate), and the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 6.42 (1H, s), 7.03-7.15 (3H, m), 7.19 (1H, s), 7.27-7.32 (3H, m), 8.12 (1H, s), 8.32-8.38 (2H, m), 9.15 (1H, s).

ESI-MS (m/e): 389 (M+H).

#### Example 117

##### 5-chloro-2-pyridine-2-yl-4,6-bis-(pyridine-3-yloxy)-1H-benzimidazole

###### Step 1

###### Synthesis of 3-chloro-2,4-bis (pyridine-3-yloxy)-nitrobenzene

To dimethylformamide 8 ml solution of [1,2,3]-trichloro-4-nitrobenzene 679 mg were added 3-hydroxypyridine 628 mg and potassium carbonate 1.82 g, and the reaction liquor was stirred at 100°C for two hours. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water, saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a straw-coloured oily substance.

###### Step 2

###### Synthesis of 3-chloro-2,4-bis (pyridine-3-yloxy) aniline

To suspension of 3-chloro-2,4-bis (pyridine-3-yloxy) nitrobenzene 1.2 g in methanol 15 ml and water 7.5 ml were added ammonium chloride 963 mg and iron powder 503 mg, and the reaction liquor was heated under reflux for three hours. The reaction liquor was eliminated by filtration, and next the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a straw-coloured oily substance.

###### Step 3

###### Synthesis of 3-chloro-2,4-bis (pyridine-3-yloxy)-6-nitroaniline

To 891 mg of 3-chloro-2,4-bis (pyridine-3-yloxy)-aniline dissolved in trifluoroacetic acid 20 ml was added potassium nitrate 315 mg, and the reaction liquor was stirred at room temperature overnight, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced

pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as orange color solid.

#### Step 4

##### Synthesis of 4-chloro-3,5-bis (pyridine-3-yloxy)-benzene-1,2-diamine

To suspension of 3-chloro-2,4-bis (pyridine-3-yloxy)-6-nitroaniline 143 mg in methanol 8 ml and water 4 ml were added ammonium chloride 128 mg and iron powder 67 mg, and the reaction liquor was heated under reflux for two hours. The reaction liquor was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as pale-brown solid.

#### Step 5

##### Production of 5-chloro-2-pyridine-2-yl-4,6-bis-(pyridine-3-yloxy)-1H-benzimidazole

4-chloro-3,5-bis (pyridine-3-yloxy)-benzene-1,2-diamine and picolinic acid were used, and it was synthesised in the same way as in Example 68, and the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 7.18-7.62 (6H, m), 7.92 and 7.99 (total 1H, each dt, J = 8.0, 1.8 Hz), 8.10-8.44 (5H, m), 8.66-8.72 (1H, m)

ESI-MS (m/e): 416, 418 (M+H).

#### Example 118

##### 5-methyl-2-pyridine-2-yl-4,6-bis-(pyridine-3-yl-oxy)-1H-benzimidazole

Using 2,4-difluoro-3-methyl nitrobenzene synthesised by a process described in Chemical and Pharmaceutical Bulletin, 1982, vol.30, issue 10, pp.3530-3543, the title compound was obtained as pale yellow solid by the same process as in Example 117, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 2.03 and 2.10 (total 3H, each s), 7.01-7.50 (6H, m), 7.88 and 7.87 (total 1H, each dt, J = 7.7, 1.6 Hz), 8.06-8.41 (5H, m), 8.63-8.70 (1H, in).

ESI-MS (m/e): 396 (M+H).

#### Example 119

##### 5-fluoro-2-pyridine-2-yl-4,6-bis-(pyridine-3-yloxy)-1H-benzimidazole

Using [1,2,3] trifluoro-4-nitrobenzene, the title compound was obtained as a straw-coloured solid by the same process as in Example 117, a process based on this or a combination of these with a normal procedure.



<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 7.21-7.63 (6H, m), 7.90-8.01 (1H, m), 8.12-8.39 (3H, m), 8.43-8.50 (2H, m), 8.63-8.73 (1H, m)

ESI-MS (m/e): 400 (M+H).

#### Example 120

##### 4-(2-cyano-phenoxy)-6-(4-N,N-dimethylcarbamoyl-phenylsulfonyl)-2-pyridine-2-yl-1H-benzimidazole

#### Step 1

##### Synthesis of 5-(4-carboxy-phenyl sulphonyl)-3-(2-cyano phenoxy)-2-nitro-phenylamine

To dimethylformamide 2 ml solution of 3-(2-cyano phenoxy)-5-fluoro-2-nitro-phenylamine 47 mg obtained in Example 78 were added 4-mercaptobenzonic acid 31 mg and potassium carbonate 55 mg, and the reaction liquor was stirred at 60°C for two hours. The reaction liquor was concentrated, and trifluoroacetic acid 1 ml was added to the residue, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as orange colored solid.

#### Step 2

##### Synthesis of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenyl sulphonyl)-2-nitro-phenylamine

To dichloromethane 2 ml solution of 5-(4-carboxy-phenyl sulphonyl)-3-(2-cyano phenoxy)-2-nitro-phenylamine 40 mg were added dimethylamine (2.0M tetrahydrofuran solution) 0.059 ml, 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 28 mg and N-hydroxybenzotriazole hydrate 20 mg, and the reaction liquor was stirred at room temperature for one hour 30 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as yellow powder.

#### Step 3

##### Synthesis of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenyl sulphonyl)- benzene-1,2-diamine

To isopropyl alcohol 2 ml solution of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenyl sulphonyl)-2-nitro-phenylamine 32 mg were added electrolytic iron powder 19 mg and saturated ammonium chloride aqueous solution 0.2 ml, and the reaction liquor was heated under reflux for two hours. After eliminating the catalyst by filtration and eliminating the solvent by distillation,

the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup>60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

#### Step 4

Synthesis of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylcarbamoyl-phenylsulfonyl)-benzene-1,2-diamine

To dichloromethane 2 ml solution of 3-(2-cyano phenoxy)-5-(4-N,N-dimethylaminocarbonyl-phenyl sulphonyl)-benzene-1,2-diamine 25 mg was added metachloroperbenzoic acid 38 mg, and the reaction liquor was stirred at room temperature for 15 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup>60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as yellow powder.

#### Step 5

Production of 4-(2-cyano-phenoxy)-6-(4-N,N-dimethylaminocarbonyl-phenylsulfonyl)-2-(pyridine-2-yl)-1H-benzimidazole

Using 3-(2-cyano phenoxy)-5-(4-N,N-dimethylaminocarbonyl-phenylsulfonyl)-benzene-1,2-diamine, the title compound was obtained as a brown solid by the same process as in Example 67 (Step 4), a process based on this or a combination of these with a normal procedure. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.91 and 2.92 (total 3H, each s), 3.10 (3H, s), 6.99 (1H, m), 7.23-7.30 (1H, m), 7.39-7.46 (2H, m), 7.50-7.58 (3H, m), 7.68-7.78 (1H, m), 7.75 and 8.33 (total 1H, each s), 7.85 and 7.92 (total 1H, each t, J = 8.4 Hz), 7.95-8.20 (2H, m), 8.39 and 8.42 (total 1H, each d, J = 8.4 Hz), 8.63-8.67 (1H, m).

ESI-MS (m/e): 524 (M+H).

#### Example 121

1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3H-benzimidazole-5-yl)-pyrrolidin-1-yl)-ethanone

#### Step 1

Synthesis of 3-bromo-4-methoxymethoxy benzoic acid ethyl ester

To tetrahydrofuran 300 ml solution of 3-bromo-4-hydroxybenzoic acid ethyl ester 20.5 g synthesised using a process described in Monatsh. Chem. 22, 1901, 437 was added sodium hydride 5.5 g under ice cooling, and the reaction liquor was stirred for 30 minutes, and thereafter, chloromethyl methyl ether 10 ml was added to the reaction liquor at the same temperature, and

the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate and washed with water, thereafter the aqueous layer was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained solid was suspended in hexane, and the title compound was obtained as a white solid.

#### Step 2

##### Synthesis of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrole-1-carboxylic acid t-butyl ester

To dimethoxyethane 350 ml of 3-bromo-4-methoxymethoxy benzoic acid ethyl ester 21 g solution were added successively 1-(t-butoxy carbonyl) pyrrole-2-boron acid 21 g, tetrakis triphenylphosphine palladium 4.2 g and sodium carbonate aqueous solution (2M) 153 ml, and under a nitrogen atmosphere, the reaction liquor was heated under reflux overnight. After cooling, the reaction liquor was diluted with water, extracted with chloroform and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 12/1-10/1), and the title compound was obtained as a white solid.

#### Step 3

##### Synthesis of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester

5 % platinum carbon catalyst 8.2 g was added to ethanol 400 ml solution of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 28.4 g, and the reaction liquor was stirred under a hydrogen atmosphere for three days. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/6.5-1/6). and the title compound was obtained as a colourless oily substance.

#### Step 4

##### Synthesis of 3-(1-acetyl-pyrrolidin-2-yl)-4-hydroxybenzoic acid ethyl ester

To mixed solution of water 50 ml and ethanol 250 ml of 2-(5-ethoxycarbonyl-2-methoxymethoxy-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 26 g was added p-toluenesulfonic acid monohydrate 13 g, and the reaction liquor was heated under reflux for two days. After cooling, the reaction liquor was diluted with water, neutralized with aqueous sodium bicarbonate and extraction with chloroform-methanol mixture medium (10/1) were carried out, and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Acetic anhydride 13 ml

was added to pyridine 200 ml solution of the obtained crude product, and the mixture was stirred. One hour was allowed to pass, and acetic anhydride 6 ml was added. Pyridine 150 ml was added after 1 hour furthermore, and triethylamine 5 ml was added further 40 minutes later. Acetic anhydride 3 ml was added further 30 minutes later, and furthermore, the reaction liquor was stirred for 30 minutes. The reaction liquor was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried using anhydrous magnesium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To methanol 200 ml solution of the obtained crude product, potassium carbonate 10 g was added, and the reaction liquor was stirred at room temperature for four hours. The reaction liquor was concentrated down by distillation under reduced pressure, and the obtained residue was diluted with saturated ammonium chloride aqueous solution and extraction was carried out with ethyl acetate. It was dried using anhydrous magnesium sulphate, and next the solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid by recovering the obtained solid by filtration with acetic acid ethyl ester.

#### Step 5

##### Synthesis of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid ethyl ester

To dimethylformamide 100 ml solution of 3-(1-acetyl-pyrrolidin-2-yl)-4-hydroxybenzoic acid ethyl ester 12.4 g were added potassium carbonate 15 g, benzyl bromide 6.4 ml, and the reaction liquor was stirred at 50°C for one hour. The reaction liquor was cooled, and thereafter, it was diluted with saturated ammonium chloride aqueous solution and extraction was carried out with ethyl acetate. The organic layer was washed with water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 10/1-1/2-1/3), and the title compound was obtained as a yellow oily substance.

#### Step 6

##### Synthesis of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid

4 N sodium hydroxide aqueous solution 23 ml was added to ethanol 200 ml solution of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid ethyl ester 18.7 g, and the reaction liquor was stirred at room temperature overnight. 4 N sodium hydroxide aqueous solution 15 ml was further added to the reaction liquor, and the reaction liquor was stirred for seven hours. The reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was diluted with water and was washed with ether. The aqueous layer was acidified using 6 N hydrochloric acid and thereafter, it was extracted with chloroform and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid.

**Step 7****Synthesis of (3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy-phenyl)-carbamic acid t-butyl ester**

Into a mixed solution of 3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy benzoic acid 5 g in toluene 15 ml and 2-methyl-2-propanol 15 ml were successively added diisopropyl ethylamine 3.0 ml and diphenylphosphoryl azide 3.8 ml and the reaction liquor was heated under reflux overnight. After cooling, saturated aqueous sodium chloride solution and saturated aqueous sodium bicarbonate were added to the reaction liquor and extraction with ethyl acetate was carried out, and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/0-1/1-0/1), and the title compound was obtained as colourless amorphous material.

**Step 8****Synthesis of 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone**

To (3-(1-acetyl-pyrrolidin-2-yl)-4-benzyloxy-phenyl)-carbamic acid t-butyl ester 4.1 g dissolved in trifluoroacetic acid 50 ml solution was added potassium nitrate 1.1 g, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and ice was added to the obtained residue, and thereafter, it was neutralized using ammonia water, and diluted with ethyl acetate. The precipitate was recovered by filtration, and crude product was obtained as a brown solid. The filtrate was diluted with saturated sodium chloride aqueous solution and was dried with anhydrous magnesium sulphate after extraction with acetic acid ethyl ester. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified using silica gel column chromatography (eluent: ethyl acetate) and the obtained solid was recovered by suspending in acetic acid ethyl ester, and crude product was obtained as brown solid. To ethanol 100 ml solution of the obtained crude product 2.8 g, hydrazine monohydrate 1.5 ml, expanded Raney nickel catalyst 1 g were added successively, and the reaction liquor was stirred at room temperature for three hours. The catalyst was eliminated by filtration by celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was diluted using saturated aqueous sodium bicarbonate and was dried with anhydrous magnesium sulphate after extraction with acetic acid ethyl ester. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform/methanol = 100/0-99/1-98/2-97/3-96/4-93/7), and the title compound was obtained as green amorphous material.

**Step 9****Synthesis of 1-(2-(6-benzyloxy-2-pyridine-2-yl)-3-(2-trimethyl silanyl-ethoxymethyl)-3H-**

benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To toluene 43 ml solution of 1-(2-(4,5-diamino-2-benzyloxy-phenyl)- pyrrolidin-1-yl)-ethanone 1.39 g was added toluene solution 3 ml of pyridine-2-carboxaldehyde 460 mg, and the reaction liquor was stirred at room temperature. After two hours, pyridine-2-carboxaldehyde 46 mg was added, and the reaction liquor was stirred at 90°C for two hours. Moreover, pyridine-2-carboxaldehyde 46 mg was added, and the reaction liquor was stirred at 90°C for ten hours. After cooling, the precipitated solid was recovered by filtration, and crude product was obtained as a brown solid. To tetrahydrofuran 20 ml solution of the obtained crude product 1.1 g, sodium hydride 144 mg, 2-(chloromethoxy) ethyl trimethylsilane 667 mg were added, and the reaction liquor was stirred at room temperature for two hours 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquid and extraction with ethyl acetate was carried out and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: ethyl acetate), and the title compound was obtained as brown amorphous material.

**Step 10**Synthesis of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilylanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To ethanol 20 ml solution of 1.18 g of 1-(2-(6-benzyloxy-2-pyridine-2-yl-3-(2-trimethylsilylanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone were added ammonium formate 713 mg, 20 % palladium hydroxide-carbon catalyst 119 mg, and the reaction liquor was heated under reflux for five hours. Ammonium formate 157 mg, 20 % palladium hydroxide-carbon catalyst 56 mg were added to the reaction liquor, and also the reaction liquor was heated under reflux for one hour. After cooling, catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was diluted with 1 N hydrochloric acid extracted with acetic acid ethyl ester and the extract dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform/methanol = 100/0-99/1-98/2), and the title compound was obtained as brown amorphous material.

**Step 11**Synthesis of 1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To pyridine 1 ml solution of 29 mg of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone were added 5-(4-bromo-phenyl)-oxazole 30 mg, cesium carbonate 56 mg and copper (II) oxide 15 mg, and

the reaction liquor was stirred at 120°C in sealed tube overnight. After cooling, saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution were added successively to the reaction liquor, extraction was carried out ethyl acetate and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under the reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 12/1), and obtained the title compound as a yellow oily substance.

#### Step 12

##### Production of 1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

1-(2-(6-(4-oxazol-5-yl-phenoxy)-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 24 mg was dissolved in trifluoroacetic acid 1 ml, and the reaction liquor was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the title compound was obtained as a yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.73-2.69 (7H, m), 3.54-3.91 (2H, m), 5.21-5.48 (1H, m), 6.91-7.98, 8.30-8.51, 8.57-8.73 (13H, each m).

ESI-MS (m/e): 466 (M+H).

#### Example 122

##### 3-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

Using 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) and 3-cyano bromobenzene, the title compound was obtained as an oily substance by the same process as in Example 121 (Step 11) (Step 12), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.42 (7H, m), 3.56-3.93 (2H, m), 5.14-5.45 (1H, m), 6.91-7.73 (7H, m), 7.80-7.96 (1H, m), 8.30-8.43 (1H, m), 8.58-8.70 (1H, m), 10.58-10.82 (1H, m)

ESI-MS (m/e): 424 (M+H).

#### Example 123

##### 3-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzamide

Using 3-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile obtained in Example 122, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.70-2.39 (7H, m), 3.39-3.89 (2H, m), 5.17-6.24 (3H, m), 6.97-7.92 (8H,

m), 8.26-8.42 (1H, m), 8.52-8.67 (1H, m), 10.42-10.72 (1H, m).

ESI-MS (m/e): 442 (M+H).

#### Example 124

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile

Using 5-bromo-pyridine-2-carbonitrile, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50-2.42 (7H, m), 3.56-3.88 (2H, m), 5.09-5.40 (1H, m), 6.89-7.92 (6H, m), 8.26-8.70 (3H, m), 10.63-11.05 (1H, m).

ESI-MS (m/e): 425 (M+H).

#### Example 125

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carboxylic acid amide

Using 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile obtained in Example 124, the title compound was obtained as an oily substance by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.60-2.42 (7H, m), 3.42-3.90 (2H, m), 4.99-5.80 (2H, m), 6.74-8.67 (10H, m), 10.42-10.10.85 (1H, m).

ESI-MS (m/e): 443 (M+H).

#### Examples 126-1, 126-2

1-(2-(6-(5-bromo-pyridine-2-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

1-(2-(6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-bromo-2-methanesulphonyl-pyridine, the title compound was respectively obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

1-(2-(6-(5-bromo-pyridine-2-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50-2.40 (7H, m), 3.50-3.87 (2H, m), 5.03-5.14, 5.31-5.42 (1H, each m), 6.71-7.88, 10.48-11.15 (7H, each m), 8.08-8.40 (2H, m), 8.50-8.69 (1H, m).

ESI-MS (m/e): 478, 480 (M+H).

1-(2-(6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone



n-1-yl)-ethanone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.57-2.59 (7H, m), 3.08-3.27 (3H, m), 3.57-3.89 (2H, m), 5.14-5.40 (1H, m), 6.94-7.64 (4H, m), 7.82-8.15 (2H, m), 8.33-8.75 (3H, m).

ESI-MS (m/e): 478 (M+H).

**Example 127**1-(2-(2-pyridine-2-yl-6-[quinoline-6-yloxy]-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-bromo-quinoline, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.67-2.69 (7H, m), 3.40-4.04 (2H, m), 5.25-5.63 (1H, m), 6.80-9.13 (12H, m), 10.22-11.44 (1H, br).

ESI-MS (m/e): 450 (M+H).

**Example 128**4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-methyl-benzonitrile

Using 4-bromo-2-methyl-benzonitrile, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.48-2.54 (10H, m), 3.20-3.89 (2H, m), 5.06-5.41 (1H, m), 6.80-8.87 (10H, m).

ESI-MS (m/e): 438 (M+H).

**Example 129**1-(2-(2-pyridine-2-yl-6-(4-trifluoromethoxy-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-bromo-4-trifluoromethoxy-benzene, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.43-2.69 (7H, m), 3.32-3.91 (2H, m), 5.20-5.59 (1H, m), 6.23-8.97 (11H, m).

ESI-MS (m/e): 483 (M+H).

**Example 130**1-(2-(2-pyridine-2-yl-6-[quinoline-3-yloxy]-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 3-bromo-quinoline, the title compound was obtained as a yellow oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.00-2.47 (7H, m), 3.37-4.00 (2H, m), 5.26-5.54 (1H, m), 6.98-9.10 (12H, m), 10.44-10.73 (1H, m)

ESI-MS (m/e): 450 (M+H).

#### Example 131

1-(2-(6-(4-acetyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(4-iodo-phenyl)-ethanone, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.47-2.60 (10H, m), 3.52-3.88 (2H, m), 5.12-5.41 (1H, m), 6.97-7.74 (6H, m), 7.80-8.02 (3H, m), 8.30-8.44 (1H, m), 8.57-8.70 (1H, m).

ESI-MS (m/e): 441 (M+H).

#### Example 132

1-(2-(6-[biphenyl-4-yloxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-bromo-biphenyl, the title compound was obtained as a yellow oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.13-2.47 (7H, m), 3.40-3.91 (2H, m), 5.20-5.60 (1H, m), 6.72-7.89 (13H, m), 8.25-8.42 (1H, m), 8.42-8.67 (1H, m), 10.29-10.60 (1H, m).

ESI-MS (m/e): 475 (M+H).

#### Example 133

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N,N-dimethyl-benzenesulphonamide

Using 4-iodo-N,N-dimethyl-benzenesulphonamide, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50-3.00 (13H, m), 3.40-3.92 (2H, m), 5.14-5.50 (1H, m), 6.40-8.80 (11H, m)

ESI-MS (m/e): 506 (M+H).

#### Example 134

1-(2-(6-[biphenyl-3-yloxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 3-bromo-biphenyl, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.80-2.50 (7H, m), 3.40-3.91 (2H, m), 5.20-5.60 (1H, m), 6.80-7.95 (13H, m)

m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 475 (M+H).

#### Example 135

1-(2-(6-(4-[propane-2-sulfonyl]-phenoxy)

2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-iodo-4-(propane-2-sulfonyl)-benzene, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.10-2.50 (13H, m), 3.05-3.30 (1H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 7.00-7.95 (8H, m), 8.30-8.50 (1H, m), 8.58-8.75 (1H, m), 10, 60-10.95 (1H, m).

ESI-MS (m/e): 505 (M+H).

#### Example 136

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzonitrile

Using 4-bromo-2-trifluoromethyl-benzonitrile, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.10-2.45 (7H, m), 3.50-3.95 (2H, m), 5.00-5.45 (1H, m), 6.60-7.95 (7H, m), 8.30-8.45 (1H, m), 8.55-8.75 (1H, m), 10.80-11.60 (1H, m).

ESI-MS (m/e): 492 (M+H).

#### Examples 137-1, 137-2

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N-ethyl-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzonitrile obtained in Example 136, the title compounds were respectively obtained by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.05-2.80 (7H, m), 3.50-4.20 (2H, m), 5.30-5.45 (1H, m), 7.30-7.80 (6H, m), 8.05-8.20 (1H, m), 8.20-8.38 (1H, m), 8.80-8.90 (1H, m).

ESI-MS (m/e): 510 (M+H).

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N-ethyl-2-trifluoromethyl-benzamide • monotrifluoroacetic acid salt

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.05-2.80 (10H, m), 3.60-4.05 (2H, m), 4.80-5.00 (2H, m), 5.30-5.45 (1H, m), 7.30-7.80 (5H, m), 8.05-8.20 (1H, m), 8.20-8.38 (1H, m), 8.80-8.90 (1H, m), 9.10-9.30 (1H, m).

ESI-MS (m/e): 538 (M+H).

#### Example 138

1-(2-(6-(4-[2-dimethylamino-ethoxy]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (2-(4-iodo-phenoxy)-ethyl)-dimethylamine, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.05-2.90 (13H, m), 3.00-4.45 (6H, m), 5.20-5.45 (1H, m), 6.80-8.00 (8H, m), 8.25-8.40 (1H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 486 (M+H).

#### Example 139

1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-bromo-benzylalcohol, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.68-2.40 (7H, m), 3.53-3.88 (2H, m), 4.62-4.72 (2H, m), 5.22-5.56 (1H, m), 6.82-7.62 (7H, m), 7.80-7.89 (1H, m), 8.32-8.40 (1H, m), 8.55-8.64 (1H, m).

ESI-MS (m/e): 429 (M+H).

#### Example 140

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N,N-dimethyl-benzamide

Using 4-bromobenzoic acid dimethyl amide, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.81-2.40 (7H, m), 2.98-3.17 (6H, m), 3.56-3.87 (2H, m), 5.20-5.53 (1H, m), 6.93-7.65 (7H, m), 7.81-7.89 (1H, m), 8.33-8.41 (1H, m), 8.60-8.67 (1H, m).

ESI-MS (m/e): 470 (M+H).

**Example 141**4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-N-methyl-benzamide

Using 4-bromo-N-methylbenzamide, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.39 (4H, m), 1.84 and 2.16 (total 3H, each s), 2.98-3.02 (3H, m), 3.58-3.74 (1H, m), 3.78-3.87 (1H, m), 5.16-5.43 (1H, m), 6.74-7.89 (8H, m), 8.36-8.39 (1H, m), 8.63-8.66 (1H, m).

ESI-MS (m/e): 456 (M+H).

**Example 142**1-(2-(2-pyridine-2-yl-6-(4-[pyrrolidine-1-carbonyl]-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (4-bromo-phenyl)-pyrrolidine-1-yl-methanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.40 (8H, m), 1.87 and 2.21 (total 3H, each s), 3.43-3.52 (2H, m), 3.60-3.71 (3H, m), 3.81-3.90 (1H, m), 5.21-5.50 (1H, m), 6.84-7.02 (2H, m), 7.25-7.58 (5H, m), 7.83-7.93 (1H, m), 8.36-8.45 (1H, m), 8.62-8.67 (1H, m).

ESI-MS (m/e): 496 (M+H).

**Example 143**1-(2-(6-(4-[morpholine-4-carbonyl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (4-bromo-phenyl)-morpholin-4-yl-methanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.78-2.62 (7H, m), 3.40-3.90 (10H, m), 5.23-5.50 (1H, m), 6.82-7.54 (7H, m), 7.86-7.94 (1H, m), 8.38-8.46 (1H, m), 8.64-8.69 (1H, m).

ESI-MS (m/e): 512 (M+H).

**Example 144**4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy) benzoic acid • monotrifluoroacetic acid salt

Using 4-bromo-benzoic acid, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.86 and 2.10 (total 3H, each s), 1.92-2.48 (4H, m), 3.41-3.90 (2H, m), 5.36-5.39 (1H, m), 7.13-7.72 (5H, m), 8.00-8.07 (3H, m), 8.22-8.26 (1H, m), 8.73-8.80 (1H, m).  
ESI-MS (m/e): 443 (M+H).

**Example 145**

1-(2-(6-(4-[piperidine-1-carbonyl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (4-bromo-phenyl)-piperidine-1-yl-methanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.45-2.40 (10H, m), 1.88 and 2.20 (total 3H, each s), 3.30-3.90 (6H, m), 5.23-5.53 (1H, m), 6.83-7.55 (7H, m), 7.84-7.94 (1H, m), 8.37-8.46 (1H, m), 8.63-8.68 (1H, m).  
ESI-MS (m/e): 510 (M+H).

**Example 146**

1-(2-(6-(4-[4-acetyl-piperazine-1-carbonyl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(4-(4-bromo-benzoyl)-piperazine-1-yl)-ethanone, the title compound was obtained as a white solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.84-2.40 (10H, m), 3.24-3.88 (10H, m), 5.22-5.48 (1H, m), 6.94-7.09 (2H, m), 7.22-7.48 (5H, m), 7.84-7.93 (1H, m), 8.37-8.43 (1H, m), 8.63-8.66 (1H, m). ESI-MS (m/e): 553 (M+H).

**Example 147**

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

**Step 1**

Synthesis of 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silanyl-ethoxymethyl)-1H-benzimidazol-5-yloxy)-benzonitrile

To N-methyl-pyrrolidinone 1 ml solution of 4-fluoro cyanobenzene 20 mg and 30 mg of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) was added sodium hydride 5.8 mg, and the reaction liquor was stirred at 100°C in sealed tube overnight. After cooling, saturated aqueous sodium bicarbonate was added to the reaction liquid and extraction with ethyl acetate was carried out, and the organic layer was washed with water and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by thin layer chromatography fractionation and recovery (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 9/1), and obtained the title compound as a yellow oily

substance.

## Step 2

Production of 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silanyl- ethoxymethyl)-1H-benzimidazol-5-yloxy)-benzonitrile, the title compound was obtained as an oily substance by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.52-2.42 (7H, m), 3.42-3.92 (2H, m), 5.02-5.40 (1H, m), 6.77-7.75 (7H, m), 7.75-7.94 (1H, m), 8.20-8.46 (1H, m), 8.50-8.69 (1H, m), 10.67-11.06 (1H, m).

ESI-MS (m/e): 424 (M+H).

## Example 148

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzamide

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)- benzonitrile obtained in Example 147, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.05-2.40 (7H, m), 3.43-3.89 (2H, m), 5.10-6.32 (3H, m), 6.88-7.90 (8H, m), 8.27-8.42 (1H, m), 8.53-8.68 (1H, m), 10.47-11.80 (1H, m).

ESI-MS (m/e): 442 (M+H).

## Example 149

2-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzonitrile

Using 2-fluoro-benzonitrile, the title compound was obtained as an oily substance by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50-2.49 (7H, m), 3.43-3.89 (2H, m), 5.10-5.34 (1H, m), 6.83-7.92 (8H, m), 8.31-8.42 (1H, m), 8.53-8.68 (1H, m), 10.80-11.23 (1H, m).

ESI-MS (m/e): 424 (M+H).

## Example 150

2-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-benzamide

Using 2-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)- benzonitrile obtained in Example 149, the title compound was obtained as an oily substance by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.52-2.46 (7H, m), 3.43-3.91 (2H, m), 5.10-5.51 (1H, m), 5.99 (1H, brs),

6.72-7.98 (8H, m), 8.26-8.43 (2H, m), 8.59-8.70 (1H, m), 10.58-10.94 (1H, m).

ESI-MS (m/e): 442 (M+H).

#### Example 151

1-(2-(6-(4-nitro-phenoxy)-2-pyridine-2-yl-3H-benzimidazole-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluoro-nitrobenzene, the title compound was obtained by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-2.50 (7H, m), 3.50-3.95, (2H, m), 5.05-5.40 (1H, m), 7.00-7.80 (5H, m), 7.80-7.95 (1H, m), 8.15-8.30 (2H, m), 8.30-8.45 (1H, m), 8.60-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 444 (M+H).

#### Example 152

1-(2-(2-pyridine-2-yl-6-(4-[2H-tetrazol-5-yl]-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole-5-yl)-benzonitrile obtained in Example 147 (Step 1), the title compound was obtained by the same process as in Example 60 and Example 121 (Step 12), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.51-2.58 (7H, m), 3.43-3.90 (2H, M), 5.09-5.55 (1H, m), 6.73-7.60, 7.69-8.04, 8.29-8.69 (10H, each m).

ESI-MS (m/e): 467 (M+H).

#### Example 153

1-(2-(6-(4-[5-methyl-[1,2,4] oxadiazol-3-yl]-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-phenyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-5-yl)-benzonitrile obtained in Example 147 (Step 1), the title compound was obtained by the same process as in Example 61, Example 64 and Example 121 (Step 12), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.49-2.7 (10H, m), 3.39-3.90 (2H, m), 5.17-5.52 (1H, m), 6.26-8.89 (11H, m).

ESI-MS (m/e): 481 (M+H).

#### Example 154

3-(4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yl)-phenyl)-4H-[1,2,4]



oxadiazole-5-one

Using 4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethylsilyl-ethoxymethyl) -1H-benzimidazol-5-yloxy)-benzonitrile obtained in Example 147 (Step 1), the title compound was obtained by the same process as in Example 61, Example 62 and Example 121 (Step 12), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.82-2.47 (7H, m), 3.60-3.3.94 (2H, m), 5.24-5.43 (1H, m), 7.15-8.05 (8H, m), 8.23-8.31 (1H, m), 8.71-8.78 (1H, m)

ESI-MS (m/e): 483 (M+H).

**Example 155**5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-1,3-dihydro-benzimidazole-2-one**Step 1**Synthesis of 1-(2-(6-[3,4-dinitro-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluoro-1,2-dinitro-benzene, the title compound was obtained as red oily substance by the same process as in Example 147 (Step 1), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.80-2.57 (7H, m), 3.61-4.02 (2H, m), 5.27-5.60 (1H, m), 6.77-7.60 (6H, m), 7.91-8.06 (1H, m), 8.17-8.33 (1H, m), 8.72 (1H, brs).

ESI-MS (m/e): 455 (M+H).

**Step 2**Synthesis of 1-(2-(6-[3,4-diamino-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To ethanol 1 ml solution of 72 mg of 1-(2-(6-[3,4-dinitro-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone were added hydrazine monohydrate 0.030 ml, expanded Raney nickel catalyst 20 mg, and the reaction liquor was stirred at room temperature for two hours. The catalyst was eliminated by filtration by celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 9/1), and obtained the title compound as brown oily substance.

**Step 3**Synthesis of 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silyl-ethoxymethyl)-1H-benzimidazol-5-yloxy)-1,3-dihydro-benzimidazole-2-one

Using 1-(2-(6-[3,4-diamino-phenoxy]-2-pyridine-2-yl-3-(2-trimethyl silyl-ethoxymethyl) -3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone, the title compound was obtained as brown oily

substance by the same process as in Example 62, a process based on this or a combination of these with a normal procedure.

#### Step 4

##### Production of 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-1,3-dihydrobenzimidazole-2-one

Using 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1-(2-trimethyl silanyl-ethoxymethyl)-1H-benzimidazol-5-yloxy)-1,3-dihydro-benzimidazole-2-one, the title compound was obtained as amorphous material by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.57 (7H, m), 3.61-4.02 (2H, m), 5.27-5.60 (1H, m), 6.77-7.60 (6H, m), 7.91-8.06 (1H, m), 8.17-8.33 (1H, m), 8.72 (1H, brs).

ESI-MS (m/e): 455 (M+H).

#### Example 156

##### 1-(2-(6-[3H-benzimidazol-5-yloxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

1-(2-(6-[3,4-diamino-phenoxy]-2-pyridine-2-yl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 155 (Step 2) 19 mg was dissolved in formic acid 1 ml, and the reaction liquor was stirred at 100°C for two hours. The reaction liquor was concentrated under reduced pressure, and the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.80-2.2.55 (7H, m), 3.60-4.00 (2H, m), 5.33-5.69 (1H, m), 7.00-7.80, 7.91-8.04, 8.16-8.30, 8.67-8.80 (10H, each m).

ESI-MS (m/e): 439 (M+H).

#### Example 157

##### 1-(2-(6-(2-methyl-3H-benzimidazol-5-yloxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using acetic acid, the title compound was obtained by the same process as in Example 156, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.69-2.63 (10H, m), 3.42-3.91 (2H, m), 5.20-5.64 (1H, m), 6.58-7.87 (9H, m), 8.22-8.66 (2H, m).

ESI-MS (m/e): 453 (M+H).

#### Example 158

##### 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyrimidine-2-carbonitr

ile

Using 5-bromo-pyrimidine-2-carbonitrile, the title compound was obtained as a white solid by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.81-2.40 (7H, m), 3.56-3.88 (2H, m), 5.08-5.34 (1H, m), 6.75-7.70 (3H, m), 7.81-7.90 (1H, m), 8.33-8.63 (4H, m).

ESI-MS (m/e): 426 (M+H).

#### Example 159

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyrimidine-2-carboxamide

Using 5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy)-pyrimidine-2-carbonitrile obtained in Example 158, it was obtained as a white solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.79-2.42 (7H, m), 3.60-3.90 (2H, m), 5.18-5.39 (1H, m), 6.99-7.71 (3H, m), 7.82-7.92 (1H, m), 8.34-8.42 (1H, m), 8.55-8.65 (3H, m).

ESI-MS (m/e): 444 (M+H).

#### Example 160

4-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yloxy) benzoic acid ethyl ester

Using 4-fluorobenzoic acid ethyl ester, it was obtained as a white solid by the same process as in Example 147, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.24-1.41 (3H, m), 1.70-2.38 (7H, m), 3.53-3.87 (2H, m), 4.32-4.41 (2H, m), 5.14-5.45 (1H, m), 6.96-7.67 (5H, m), 7.82-7.91 (1H, m), 7.98-8.06 (2H, m), 8.34-8.43 (1H, m), 8.61-8.68 (1H, m).

ESI-MS (m/e): 471 (M+H).

#### Example 161

1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

##### Step 1

Synthesis of 1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To tetrahydrofuran 1 ml solution of 29.2 mg of 1-(2-(6-hydroxy-2-pyridine-2-yl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) were added successively diisopropylamine 0.019 ml, triphenyl phosphine 27.6 mg, 2-phenyl-ethanol 0.011 ml, and the

reaction liquor was stirred at room temperature for six hours. Diisopropylamine 0.040 ml, triphenyl phosphine 53.2 mg, 2-phenyl-ethanol 0.023 ml were added successively to the reaction liquor, and the reaction liquor was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquor, extracted with acetic acid ethyl ester and dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), ethyl acetate), and obtained the title compound as brown oily substance.

### Step 2

Production of 1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(2-(6-phenethyl oxy-2-pyridine-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone, the title compound was obtained as an oily substance by the same process as in Example 121 (Step 12), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.59-2.23 (7H, m), 2.87-3.10, 3.50-3.86, 3.96-4.35 (6H, each m), 5.04-5.13, 5.46-5.57 (1H, each m), 6.53-7.55 (8H, m), 7.77-7.89 (1H, m), 8.32-8.40 (1H, m), 8.54-8.65 (1H, m), 10.73-11.14 (1H, m)

ESI-MS (m/e): 4271 (M+H).

### Example 162

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

#### Step 1

Synthesis of 2-(2-fluoro-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester

To a mixed solution of 3-bromo-4-fluoro-nitrobenzene 4.3 g, dimethoxyethane 130 ml of 1-(t-butoxy carbonyl) pyrrole-2-boron acid 5.0 g and water 22 ml, tetrakis triphenylphosphine palladium 1.1 g, sodium carbonate 4.2 g were added and the reaction liquor was heated under reflux overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquid and the liquid was extracted with ethyl acetate, and the organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane/ethyl acetate = 20/1), and the title compound was obtained as a yellow oily substance.

#### Step 2

Synthesis of 2-((2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1-carboxylic acid

t-butyl ester

To 2-(2-fluoro-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 2.5 g and 4-methanesulphonyl-phenol 1.55 g dissolved in dimethylformamide 20 ml was added potassium carbonate 3.38 g, and the reaction liquor was stirred at 100°C for two hours. After cooling, water was added to the reaction liquid and the liquid was extracted with ethyl acetate, washed with water and saturated aqueous sodium chloride solution, and the organic layer was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1), and the title compound was obtained as a straw-coloured solid.

## Step 3

Synthesis of 2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester

To ethanol solution 120 ml of 2-((2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 2.87 g was added 5 % platinum carbon catalyst 1.0 g, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a white solid.

## Step 4

Synthesis of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone

Zinc powder 342 mg and chloroformic acid benzyl ester 650 mg were added to benzene 25 ml solution of 2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 1.51g, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was filtered with celite, and saturated aqueous sodium bicarbonate was added to filtrate, extracted with ethyl acetate, and the organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained crude product was dissolved in 4 N hydrochloric acid-1,4-dioxane 20 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the obtained crude product was dissolved in chloroform 30 ml, and pyridine 2 ml and anhydrous trifluoroacetic acid 0.5 ml were added under ice cooling, and the reaction liquor was stirred at room temperature for two hours. 1 N hydrochloric acid was added to the reaction liquid and the liquid was extracted with ethyl acetate, and washed with water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and

the organic layer was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and 10 % palladium-carbon catalyst 50 mg was added to methanol 100 ml solution of the obtained crude product, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-1/3), and the title compound was obtained as a white solid.

#### Step 5

Synthesis of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-4-nitro-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone

To trifluoroacetic acid 2 ml solution of 588 mg of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone was added potassium nitrate 153 mg, and the reaction liquor was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and it was neutralized and thereafter, it was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained as yellow solid.

#### Step 6

Synthesis of 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To ethanol 10 ml solution of 521 mg of 1-(2-(5-amino-2-(4-methanesulphonyl-phenoxy)-4-nitro-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone was added expanded Raney nickel catalyst 100 mg, and under a hydrogen atmosphere, the reaction liquor was stirred overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To methanol 10 ml solution of the obtained crude product 448 mg, pyridine-2-carboxaldehyde 226 mg was added, and the reaction liquor was stirred at 50°C overnight.

Water was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform / methanol = 20/1), and the title compound was obtained as a straw-coloured solid.

**Step 7****Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole**

To mixed solution of water 3 ml and methanol 16 ml of 375 mg 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone was added potassium carbonate 500 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was concentrated down by distillation under reduced pressure, and saturated aqueous sodium bicarbonate was added and diluted, and thereafter, it was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate.

The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform / methanol / ammonia water = 10/1/0.1), and the title compound was obtained as a straw-coloured solid.

**Step 8****Production of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**

To methylene chloride 1 ml solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole 10 mg, acetic anhydride 0.003 ml was added, and thereafter the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.40 (7H, m), 3.05 and 3.08 (total 3H, each s), 3.52-3.90 (2H, m), 5.13-5.37 (1H, m), 7.08-7.69 (5H, m), 7.83-7.97 (3H, m), 8.32-8.40 (1H, m), 8.61-8.70 (1H, m).

ESI-MS (m/e): 477 (M+H).

**Example 163****1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B**

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol 230 mg obtained in Example 162 (Step 7) was optically-resolved using a column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / 2-propanol / diethylamine 20/80/0.1, flow rate: 10 ml/min), and enantiomer A (retention time: 19.0 min), enantiomer B (retention time: 32.2 min) were respectively obtained as yellow oily substance.

**Example 164**1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone A

To methylene chloride 1 ml solution of 12 mg of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A obtained in Example 163 was added acetic anhydride 0.003 ml, and thereafter the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound, one of chiral body was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.40 (7H, m), 3.05 and 3.08 (total 3H, each s), 3.52-3.90 (2H, m), 5.13-5.37 (1H, m), 7.08-7.69 (5H, m), 7.83-7.97 (3H, m), 8.35-8.43 (1H, m), 8.61-8.70 (1H, m).

ESI-MS (m/e): 477 (M+H).

Specific rotation:  $[\alpha]^{24}_D$  (c = 0.100, ethanol) -46.9°C.

**Example 165**1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone B

To methylene chloride 1 ml solution of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B 44 mg obtained in Example 163 was added acetic anhydride 0.011 ml, and thereafter the reaction liquor was stirred at room temperature for one hour. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound, one of chiral body as a white solid.

ESI-MS (m/e): 477 (M+H).

Specific rotation:  $[\alpha]^{24}_D$  (c = 0.100, ethanol) +47.7°C.

**Example 166**2,2,2-trifluoro-1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluorophenol, the title compound was obtained as a white solid by process same as in Example 162 (Step 2)-(Step 6), a process based on these or combining these and the normal method.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.96-2.21 (3H, m), 2.31-2.43 (1H, m), 3.77-4.08 (2H, m), 5.47-5.70 (1H, m), 6.88-6.91 (1H, m), 7.00-7.08 (4H, m), 7.26-7.50 (2H, m), 7.82-7.85 (1H, m), 8.31-8.35 (1H,



m), 8.57-8.61 (1H, m).

ESI-MS (m/e): 471 (M+H).

#### Example 167

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-fluorophenol, the title compound was obtained as a white solid by process same as in Example 162 (Step 2)-(Step 8), a process based on these or combining these and the normal method.

<sup>1</sup>HNM (CDCl<sub>3</sub>) δ : 1.83-2.03 (6H, m), 2.32-2.41 (1H, m), 3.58-3.86 (2H, m), 5.26-5.57 (1H, m), 6.96-7.06 (5H, m), 7.24-7.35 (2H, m), 7.80-7.88 (1H, m), 8.30-8.37 (1H, m), 8.56-8.62 (1H, m).

ESI-MS (m/e): 417 (M+H).

#### Example 168

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-hydroxy-ethanone

Using 4-fluorophenol, to chloroform 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same process as in Example 162 (Step 2)-(Step 7) were added successively glycolic acid 4.5 mg, N-hydroxybenzotriazole hydrate 12.3 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 15.4 mg, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.88-2.13 (3H, m), 2.20-2.43 (1H, m), 3.40-4.21 (4H, m), 5.14-5.60 (1H, m), 6.85-7.54 (7H, m), 7.78-7.86 (1H, m), 8.29-8.37 (1H, m), 8.56-8.61 (1H, m).

ESI-MS (m/e): 433 (M+H).

#### Example 169

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methoxy-ethanone

Using methoxyacetic acid, it was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.41 (4H, m), 3.26-3.46 (3H, m), 3.52-4.16 (4H, m), 5.28-5.60 (1H, m), 6.79-7.57 (7H, m), 7.77-7.85 (1H, m), 8.28-8.38 (1H, m), 8.56-8.62 (1H, m)

ESI-MS (m/e): 447 (M+H).

#### Example 170

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-phenyl-propanone

pane-1-one

Using 3-phenyl-propionic acid, it was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.82-3.03 (8H, m), 3.48-3.93 (2H, m), 5.13-5.99 (1H, m), 6.82-7.60 (12H, m), 7.80-7.08 (1H, m), 8.09-8.39 (1H, m), 8.56-8.66 (1H, m).

ESI-MS (m/e): 507 (M+H).

**Example 171**(2-(6-[4-fluoro-phenoxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-(2R)-pyrrolidin e-2-yl-methanone

To chloroform 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively 1-t-butoxy carbonyl-D-proline 13.8 mg, N-hydroxybenzotriazole hydrate 12.3 mg and 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride 15.4 mg, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and thereafter the obtained residue was dissolved in 4 N hydrochloric acid-ethyl acetate solution 1 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by thin layer chromatography (NH TLC plate (FUJI SILYSIA CHEMICAL Co.), chloroform /methanol = 30/1), and the title compound was obtained as oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.82-4.00 (13H, m), 5.23-5.61 (1H, m), 6.82-7.59 (7H, m), 7.78-7.88 (1H, m), 8.32-8.39 (1H, m), 8.57-8.64 (1H, m).

ESI-MS (m/e): 472 (M+H).

**Example 172**(2-(6-[4-fluoro-phenoxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-(2S)-pyrrolidin e-2-yl-methanone

Using 1-t-butoxycarbonyl-L-proline, the title compound was obtained as oily substance by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.82-4.00 (13H, m), 5.23-5.61 (1H, m), 6.82-7.59 (7H, m), 7.78-7.88 (1H, m), 8.30-8.39 (1H, m), 8.57-8.64 (1H, m).

ESI-MS (m/e): 472 (M+H).

**Example 173**2-dimethylamino-1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using N,N-dimethylglycine hydrochloride, it was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.81-2.57 (10H, m), 2.76-3.96 (4H, m), 5.41-5.62 (1H, m), 6.94-7.37 (7H, m), 7.81-7.89 (1H, m), 8.33-8.38 (1H, m), 8.59-8.68 (1H, m).

ESI-MS (m/e): 460 (M+H).

#### Example 174

1-(2-(6-[4-fluoro-phenoxy]-2-pyridine-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-propane-1-one

Using propionic acid, the title compound was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.95-1.24 (3H, m), 1.70-2.60 (6H, m), 3.52-3.94 (2H, m), 5.24-5.62 (1H, m), 6.75-7.66 (7H, m), 7.77-7.92 (1H, m), 8.27-8.44 (1H, m), 8.52-8.68 (1H, m), 10.66-11.08 (1H, m)

ESI-MS (m/e): 431 (M+H).

#### Example 175

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-butane-1-one

Using n-butyric acid, the title compound was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.70-1.07 (3H, m), 1.40-2.44 (8H, m), 3.53-3.91 (2H, m), 5.25-5.60 (1H, m), 6.72-7.66 (7H, m), 7.80-7.93 (1H, m), 8.30-8.44 (1H, m), 8.53-8.68 (1H, m), 10.68-11.18 (1H, m).

ESI-MS (m/e): 445 (M+H).

#### Example 176

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-hydroxypropane-1-one

Using 3-hydroxypropionic acid, the title compound was obtained as an oily substance by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.43-2.73 (6H, m), 3.24-4.27 (5H, m), 5.24-5.60 (1H, m), 6.75-7.60 (7H, m), 7.76-7.88 (1H, m), 8.27-8.40 (1H, m), 8.53-8.66 (1H, m), 10.44-11.01 (1H, m).

ESI-MS (m/e): 447 (M+H).

#### Example 177

1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylami

no-ethanone

Using N-t-butoxycarbonyl-N-methylglycine, the title compound was obtained by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.82-2.01 (3H, m), 2.43-2.56 (4H, m), 3.25-4.15 (4H, m), 5.32-5.37 (1H, m), 7.00-7.31 (4H, m), 7.38-7.58 (2H, m), 8.03-8.08 (1H, m), 8.37-8.43 (1H, m), 8.69-8.79 (1H, m), 8.80-8.94 (1H, m).

ESI-MS (m/e): 446 (M+H).

**Example 178**5-(4-fluoro-phenoxy)-6-(1-methansulphonyl-pyrrolidine-2-yl)-2-pyridine-2-yl-1H-benzimidazole

To ethyl acetate 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively triethylamine 0.01 ml and methane sulphonyl chloride 0.005 ml, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.08 (3H, m), 2.28-2.42 (1H, m), 2.81 and 2.84 (total 3H, each s), 3.47-3.74 (2H, m), 5.17-5.37 (1H, m), 6.79-7.93 (8H, m), 8.30-8.37 (1H, m), 8.57-8.61 (1H, m).

ESI-MS (m/e): 453 (M+H).

**Example 179**5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-(1-pyrimidine-2-yl-pyrrolidin-2-yl)-1H-benzimidazole

To ethanol 2 ml solution of 17.1 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively triethylamine 0.013 ml and 2-chloro-pyrimidine 6.3 mg, and the reaction liquor was heated under reflux for three hours. The reaction solvent was eliminated by distillation under reduced pressure, and next, the obtained residue was refined by reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the obtained fraction was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, and thereafter, was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as white individual(sic).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.98-2.15 (3H, m), 2.34-2.42 (1H, m), 3.68-3.78 (1H, m), 3.90-4.07 (1H, m), 5.63 (1H, d, J = 8.0 Hz), 6.43 (1H, brs), 6.87-7.55 (7H, m), 7.79-7.84 (1H, m), 8.15-8.34 (3H, m), 8.55-8.58 (1H, m).

ESI-MS (m/e): 453 (M+H).

**Example 180**2-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-acetamide

To acetonitrile 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively potassium carbonate 11.4 mg and iodoacetamide 11.1 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was concentrated, thereafter the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid) and the obtained fraction was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as white individual(sic).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.04 (3H, m), 2.20-2.13 (1H, m), 2.80-2.85 (1H, m), 3.37-3.44 (2H, m), 3.96-4.03 (1H, m), 5.41-5.52 (1H, m), 6.90-7.34 (5H, m), 7.36-7.39 (1H, m), 7.65 and 8.00 (total 1H, each s), 7.83-7.87 (1H, m), 8.36-8.39 (1H, m), 8.59-8.64 (1H, m).

ESI-MS (m/e): 432 (M+H).

**Example 181**2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid ethyl ester

To benzene 1 ml solution of 20 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 168 were added successively zinc powder 5.2 mg and ethyl chloroformate 0.006 ml, and the reaction liquor was stirred at room temperature overnight. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.23-1.31 (3H, m), 1.80-2.00 (3H, m), 2.20-2.39 (1H, m), 3.50-3.79 (2H, m), 3.91-4.17 (2H, m), 5.17-5.38 (1H, m), 6.81-7.63 (7H, m), 7.77-7.85 (1H, m), 8.28-8.39 (1H, m), 8.55-8.63 (1H, m).

ESI-MS (m/e): 447 (M+H).

**Example 182**2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide

To methylene chloride 1 ml solution of 17.1 mg of

5-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) were added successively dimethylamino pyridine 5 mg and isocyanic acid trimethylsilyl ester 0.029 ml, and the reaction liquor was stirred at room temperature overnight. Water was added to the reaction liquid and the liquid was extracted with ethyl acetate and thereafter, was washed with saturated aqueous sodium chloride solution. After drying and concentration, the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid) and the obtained fraction was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.83-2.09 (3H, m), 2.22-2.40 (1H, m), 3.07 (3H, s), 3.56-3.82 (2H, m), 4.35 and 4.62 (total 2H, each brs), 5.01-5.20 (1H, m), 7.08-7.95 (8H, m), 8.34-8.40 (1H, m), 8.62-8.64 (1H, m).

ESI-MS (m/e): 478 (M+H).

#### Examples 183-1, 183-2

##### 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide enantiomer A and enantiomer B

The racemic body 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide 10 mg obtained in Example 182 was optically-resolved using a column for optical resolution (CHIRALPAK AD 2 cm $\phi$  x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane/ ethanol 20/80, flow rate: 10 ml/min), and enantiomer A (retention time: 17.9 min), enantiomer B (retention time: 27.6 min) were respectively obtained as white solid.

Enantiomer A.

ESI-MS (m/e): 478 (M+H).

Specific rotation:  $[\alpha]^{24}_D$  (c = 0.100, ethanol) -27.4°C.

Enantiomer B.

ESI-MS (m/e): 478 (M+H).

Specific rotation:  $[\alpha]^{24}_D$  (c = 0.100, ethanol) +28.4°C.

#### Example 184.

##### 2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide

To methylene chloride 1 ml solution of 31.2 mg of 5-(4-fluoro-phenoxy)-2-pyridine-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example

168 were added successively dimethylaminopyridine 2 mg and isocyanic acid trimethylsilyl ester 0.059 ml, and the reaction liquor was stirred at room temperature overnight. Water was added to the reaction liquid and the liquid was extracted with ethyl acetate and thereafter the extract washed with saturated aqueous sodium chloride solution. After drying and concentration, the obtained residue was refined by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.88-2.08 (3H, m), 2.32-2.48 (1H, m), 3.62-3.87 (2H, m), 4.34 and 4.71 (total 2H, each brs), 5.15-5.30 (1H, m), 6.91-7.73 (7H, m), 7.81-7.87 (1H, m), 8.31-8.37 (1H, m), 8.59-8.61 (1H, m).

ESI-MS (m/e): 418 (M+H).

#### Examples 185-1, 185-2

##### 2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide enantiomer A and enantiomer B

The racemic body 2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide 9.0 mg obtained in Example 184 was optically-resolved by a column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / 2-propanol 50/50, flow rate: 10 ml/min), and enantiomer A (retention time: 12.1 min), enantiomer B (retention time: 26.9 min) were respectively obtained as white solid.

Enantiomer A.

ESI-MS (m/e): 418 (M+H).

Enantiomer B.

ESI-MS (m/e): 418 (M+H).

#### Example 186

##### 2-(6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide

Using 4-hydroxy-N,N-dimethyl-benzamide, the title compound was obtained as a white solid by the same process as in Example 162 (Step 2)-(Step 7) and Example 182, a process based on these or a combination of these with a normal procedure..

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.85-2.07 (3H, m), 2.28-2.43 (1H, m), 3.00-3.18 (6H, m), 3.60-3.80 (2H, m), 5.10-5.23 (1H, m), 7.01-7.76 (7H, m), 7.83-7.88 (1H, m), 8.33-8.39 (1H, m), 8.63-8.64 (1H, m).

ESI-MS (m/e): 471 (M+H).

**Examples 187-1, 187-2****2-(6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide enantiomer A and enantiomer B**

2-(6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxamide 72.2 mg of racemic body obtained in Example 186 was optically-resolved by a column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol 40/60, flow rate: 10 ml/min), and enantiomer A (retention time: 18.1 min), enantiomer B (retention time: 23.9 min) were respectively obtained as white solid.

Enantiomer A.

ESI-MS (m/e): 471 (M+H).

Enantiomer B.

ESI-MS (m/e): 471 (M+H).

**Example 188****2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid ethyl ester amide**

Using isocyanic acid ethyl ester, the title compound was obtained as a white solid by the same process as in Example 184, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.94-1.07 (3H, m), 1.80-2.03 (3H, m), 2.25-2.41 (1H, m), 3.10-3.26 (2H, m), 3.57-3.74 (2H, m), 4.02-4.14 (1H, m), 5.07-5.23 (1H, m), 6.85-7.66 (7H, m), 7.78-7.85 (1H, m), 8.30-8.38 (1H, m), 8.54-8.63 (1H, m).

ESI-MS (m/e): 446 (M+H).

**Example 189****1-(2-(6-(4-fluoro-phenoxy)-2-pyrazine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**

Using pyrazine-2-carboxaldehyde, the title compound was obtained as a white solid by the same process as in Example 162 (Step 6)-(Step 8), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.86-2.08 (7H, m), 3.37-3.90 (2H, m), 5.27-5.55 (1H, m), 6.76-7.64 (6H, m), 8.32-8.62 (2H, m), 9.53-9.56 (1H, m).

ESI-MS (m/e): 418 (M+H).

**Example 190****1-(2-(6-(4-fluoro-phenoxy)-2-thiazol-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**



Using thiazole-2-carboxaldehyde, it was obtained as a white solid by the same process as in Example 162 (Step 6)-(Step 8), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.23 (6H, m), 2.24-2.43 (1H, m), 3.50-3.88 (2H, m), 5.28-5.57 (1H, m), 6.64-7.62 (7H, m), 7.89-7.94 (1H, m).

ESI-MS (m/e): 423 (M+H).

#### Example 191

1-(6-[4-methanesulphonyl-phenoxy]-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-methanol

Using D,L-prolinol, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.64-1.92 (3H, m), 1.97-2.06 (1H, m), 3.00-3.12 (1H, m), 3.04 (3H, s), 3.38-3.46 (1H, m), 3.53-3.64 (2H, m), 3.84 (1H, brs), 6.98 (2H, d, J = 8.6 Hz), 7.10 and 7.22 (total 1H, each s), 7.33-7.40 (1H, m), 7.50-7.57 (1H, m), 7.80-7.90 (3H, m), 8.34-8.41 (1H, m), 8.62-8.63 (1H, m)

ESI-MS (m/e): 465 (M+H).

#### Example 192

1-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxylic acid methyl ester

Using D,L-proline methyl ester hydrochloride, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.83-2.03 (3H, m), 2.20-2.28 (1H, m), 3.05 (3H, s), 3.20-3.86 (2H, m), 3.54 (3H, s), 4.28-4.53 (1H, m), 6.91-7.37 (3H, m), 7.32-7.38 (2H, m), 7.81-7.87 (3H, m), 8.30-8.39 (1H, m), 8.61-8.62 (1H, m).

ESI-MS (m/e): 493 (M+H).

#### Example 193

1-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxylic acid methyl ester amide

Using DL-proline methyl amide hydrochloride, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.03 (3H, m), 2.25-2.40 (1H, m), 2.46-2.53 (3H, m), 3.06 (3H, s), 3.20-3.26 (1H, m), 3.60-3.78 (1H, m), 4.18-4.24 (1H, m), 7.02-7.60 (3H, m), 7.03 (2H, d, J = 9.0 Hz), 7.82-7.92 (1H, m), 7.89 (2H, d, J = 9.0 Hz), 8.35 (1H, d, J = 7.4 Hz), 8.63 (1H, d, J = 4.7

Hz).

ESI-MS (m/e): 492 (M+H).

#### Example 194

##### 1-(6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using DL-prolin amide hydrochloride, it was obtained as a white solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.91-2.03 (3H, m), 2.26-2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18-3.28 (1H, m), 3.63-3.91 (1H, m), 4.13-4.29 (1H, m), 6.04-6.33 (1H, m), 6.86-7.28 (4H, m), 7.37-7.41 (1H, m), 7.48-7.54 (1H, m), 7.80-7.92 (3H, m), 8.34-8.38 (1H, m), 8.48-8.63 (1H, m)

ESI-MS (m/e): 478 (M+H).

#### Example 195

##### 1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-piperidine-1-yl)-ethanone

###### Step 1

###### Synthesis of 2-(2-(4-fluoro-5-nitro-phenyl)-pyridine

Tetrakis triphenylphosphine palladium 0.55 g was added to 1,4-dioxane 20 ml solution of 2-trimethyl tin-pyridine 2.3 g and 3-bromo-4-fluoro-nitrobenzene 2.1 g and the reaction liquor was heated under reflux overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 7/1), and the title compound was obtained as yellow solid.

###### Step 2

###### Synthesis of 2-(2-(4-fluoro-phenoxy)-5-nitro-phenyl)-pyridine

To dimethylformamide 10 ml solution of 4-fluoro-phenol 347 mg and 4-fluoro-3-pyridyl nitrobenzene 600 mg was added potassium carbonate 713 mg, and the reaction liquor was stirred at 100°C for one hour. After cooling, water was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1), and the title compound was obtained as a straw-coloured solid.

###### Step 3

Synthesis of (4-(4-fluoro-phenoxy-3-pyridine-2-yl-phenyl)-carbamic acid t-butyl ester

10 % palladium-carbon catalyst 100 mg was added to ethyl acetate 10 ml solution of 2-(2-(4-fluoro-phenoxy)-5-nitro-phenyl)-pyridine 840 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To tetrahydrofuran 10 ml solution of the obtained crude product, di-t-butyl dicarbonate 1.5 g was added, and the reaction liquor was stirred at 60°C overnight. The reaction liquor was cooled, and thereafter the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 10/1), and the title compound was obtained as a white solid.

**Step 4**Synthesis of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-phenyl)-piperidine-1-yl)-ethanone

To ethanol 20 ml solution of (4-(4-fluoro-phenoxy-3-pyridine-2-yl-phenyl)-carbamic acid t-butyl ester 300 mg were added acetic anhydride 0.3 ml and 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the filtrate was eliminated by distillation under reduced pressure, and the crude product was obtained. The obtained crude product was dissolved in 4 N hydrochloric acid-1,4-dioxane 5 ml, and the reaction liquor was stirred at room temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction with ethyl acetate was carried out, and the organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate), and the title compound was obtained as a straw-coloured solid.

**Step 5**Synthesis of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-4-nitro-phenyl)-piperidine-1-yl)-ethanone

To trifluoroacetic acid 1 ml solution of 190 mg of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-phenyl)-piperidine-1-yl)-ethanone was added potassium nitrate 64 mg, and the reaction liquor was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added to the reaction liquor and neutralization caused, and thereafter, it was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained as yellow solid.

## Step 6

Production of 1-(2-(6-(4-fluoro-phenoxy)-2-pyridine-2-yl-3H-benzimidazol-5-yl)-piperidine-1-yl)-ethanone

To ethanol 10 ml solution of 180 mg of 1-(2-(5-amino-2-(4-fluoro-phenoxy)-4-nitro-phenyl)-piperidine-1-yl)-ethanone was added expanded Raney nickel catalyst 50 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration with celite, and the filtrate was eliminated by distillation under reduced pressure, and crude product 171 mg was obtained. The obtained crude product 50 mg was dissolved in N-methylpyrrolidone 1 ml, and pyridine-2-carboxaldehyde 16 mg was added, and the reaction liquor was stirred at room temperature for three days. Water was added to the reaction liquid and the liquid extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the reaction mixture was purified using reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (made by YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid), and the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-1.85 (3H, m), 1.92-2.09 (5H, m), 2.22-2.30 (1H, m), 3.50-3.78 (2H, m), 5.35-5.38 (1H, m), 6.94-7.08 (5H, m), 7.32-7.38 (2H, m), 7.84-7.89 (1H, m), 8.35-8.38 (1H, m), 8.62-8.67 (1H, m).

ESI-MS (m/e): 431 (M+H).

## Example 196

5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

## Step 1

Synthesis of (3-fluoro-4-hydroxy-phenyl)-carbamic acid tert-butyl ester

To 3-fluoro-4-hydroxy nitrobenzene 6.15 g and methanol 100 ml solution of di-tert-butyl carbonate 930 mg, 10 % palladium-carbon catalyst 600 mg was added, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure, and, by the residue obtained by recovering by filtration with ethyl acetate-hexane mixed solvent, the title compound was obtained.

## Step 2

Synthesis of (3-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-phenyl)-carbamic acid tert-butyl ester

To N-methylpyrrolidinone 50 ml solution of (3-fluoro-4-hydroxy-phenyl)-carbamic acid

tert-butyl ester 4.74 g obtained in (Step 1) were added 5-chloro-2-methanesulphonyl-pyridine 4.00 g and cesium carbonate 8.80 g, and the reaction liquor was stirred at 100°C for two hours. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained.

### Step 3

#### Synthesis of 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine

To trifluoroacetic acid 35 ml solution of (3-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-phenyl)-carbamic acid tert-butyl ester 3.38 g obtained in (Step 2) was added potassium nitrate 0.98 g, and the reaction liquor was stirred at room temperature for one hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2), and the title compound was obtained.

### Step 4

#### Synthesis of 5-(2-cyano-phenoxy)-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine

To N-methylpyrrolidinone 2 ml solution of 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine 150 mg obtained in (Step 3) were added potassium carbonate 70 mg and 2-hydroxy-benzonitrile 60 mg, and the reaction liquor was stirred at 90°C for five hours. Water was added to the reaction liquor, and thereafter the title compound was obtained by recovering the precipitate by filtration.

### Step 5

#### Synthesis of 4-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine

To methanol 5 ml solution of 5-(2-cyano-phenoxy)-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine 161 mg obtained in (Step 4) was added expanded Raney nickel catalyst 20 mg, and the reaction liquor was stirred under a hydrogen atmosphere overnight. The catalyst was eliminated by filtration and thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

## Step 6

Production of 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To methanol 1 ml solution of 4-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 37 mg obtained in (Step 5) were added pyridine-2-carboxaldehyde 0.007 ml and nitrobenzene 0.5 ml, and the reaction liquor was stirred at 120°C overnight. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by silica gel column chromatography (eluent: chloroform / methanol = 20/1) and by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as a brown solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.20 (3H, s), 6.94 (1H, d, J = 7.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.41-7.47 (1H, m), 7.47 (1H, t, J = 7.8 Hz), 7.53 (1H, dd, J = 7.8, 2.3 Hz), 7.56-7.61 (1H, m), 7.66 (1H, d, J = 7.8 Hz), 7.72 (1H, s), 7.78 (1H, s), 8.04 (1H, d, J = 7.8 Hz), 8.26 (1H, d, J = 2.3 Hz), 8.35 (1H, d, J = 7.8 Hz), 8.80 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 484 (M+H).

## Example 197

5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To dimethylformamide 2 ml solution of 4-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 72 mg obtained in Example 196 (Step 5) were added pyrazine-2-carboxylic acid 21 mg, hydroxybenzotriazole 52 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 52 mg, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was dissolved in N-methylpyrrolidinone 1 ml, and ytterbium tri (trifluoromethane sulfonate) 20 mg was added, and the reaction liquor was stirred at 160°C for two hours. The reaction liquor was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by silica gel column chromatography (eluent: chloroform / methanol = 30/1) and by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a brown solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.20 (3H, s), 6.93 (1H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.43 (1H, dd, J = 8.6, 2.3 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.67-7.90 (2H, m), 8.03 (1H, d, J = 8.6 Hz), 8.25 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 2.3 Hz), 8.81 (1H, d, J = 2.3 Hz),

9.53 (1H, s).

ESI-MS (m/e): 485 (M+H).

#### Example 198

5-(2-carbamoyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole obtained in Example 196, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.23 (3H, s), 6.85-6.91 (1H, m), 7.17 (1H, t, J = 7.8 Hz), 7.40-7.45 (2H, m), 7.53 (1H, dd, J = 7.8, 4.3 Hz), 7.55-7.78 (1H, m), 7.88 (1H, dd, J = 7.8, 2.3 Hz), 7.99 (1H, d, J = 8.6 Hz), 8.02 (1H, td, J = 7.8, 2.3 Hz), 8.27 (1H, d, J = 2.3 Hz), 8.34 (1H, d, J = 7.8 Hz), 8.78 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 502 (M+H).

#### Example 199

5-(2-carbamoyl-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole obtained in Example 197, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.22 (3H, s), 6.87-6.91 (1H, m), 7.15-7.22 (1H, m), 7.41-7.46 (2H, m), 7.51-7.85 (2H, m), 7.87 (1H, dd, J = 7.8, 2.3 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.25-8.28 (1H, m), 8.73-8.75 (1H, m), 8.80-8.82 (1H, m), 9.51-9.54 (1H, m).

ESI-MS (m/e): 503 (M+H).

#### Example 200

5-(2-fluoro-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-fluorophenol, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.20 (3H, s), 6.97-7.04 (1H, m), 7.05-7.15 (3H, m), 7.33 (1/2H, dd, J = 8.8, 2.8 Hz), 7.34 (1/2H, dd, J = 8.8, 2.8 Hz), 7.36-7.42 (1H, m), 7.42 (1/2H, s), 7.70 (1/2H, s),

7.86-7.91 (1H, m), 7.99 (1/2H, d, J = 8.8 Hz), 8.00 (1/2H, d, J = 8.8 Hz), 8.34-8.40 (1H, m), 8.44 (1H, d, J = 2.8 Hz), 8.61-8.65 (1H, m), 10.85 (1/2H, brs), 10.96 (1/2H, brs)  
ESI-MS (m/e): 477 (M+H).

**Example 201****5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole**

Using pyrazine-2-carboxylic acid and 4-(2-fluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 200, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.21 (3H, s), 7.02-7.08 (1H, m), 7.09-7.17 (3H, m), 7.11 (1/2H, s), 7.34 (1/2H, dd, J = 8.6, 2.7 Hz), 7.36 (1/2H, dd, J = 8.6, 2.7 Hz), 7.42 (1/2H, s), 7.43 (1/2H, s), 7.74 (1/2H, s), 8.01 (1/2H, d, J = 8.6 Hz), 8.02 (1/2H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.58 (1/2H, dd, J = 2.7, 1.6 Hz), 8.60 (1/2H, dd, J = 2.7, 1.6 Hz), 8.67 (1/2H, d, J = 2.7 Hz), 8.68 (1/2H, d, J = 2.7 Hz), 9.59 (1/2H, d, J = 1.6 Hz), 9.62 (1/2H, d, J = 1.6 Hz), 10.47 (1/2H, brs), 10.61 (1/2H, brs)

ESI-MS (m/e): 478 (M+H).

**Example 202****5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole**

To dimethylformamide 0.5 ml solution of 4-(2-fluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 15 mg obtained in Example 200 was added 1H-pyrazole-3-carboxaldehyde 3.9 mg, and the reaction liquor was stirred at 90°C for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 9/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.20 (3H, s), 6.94-6.99 (1H, m), 7.01-7.15 (4H, m), 7.25-7.65 (2H, m), 7.31 (1H, dd, J = 8.9, 2.7 Hz), 7.66 (1H, d, J = 2.3 Hz), 7.98 (1H, d, J = 8.9 Hz), 8.40 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 466 (M+H).

**Example 203****5-(2-fluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole**

To dimethylformamide 0.5 ml solution of 4-(2-fluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 15 mg obtained in Example 200



were added 1-methyl-1H-pyrazole-3-carboxylic acid 4.3 mg, hydroxybenzotriazole 6.0 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 8.5 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with chloroform and was washed using water, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and p-toluenesulfonic acid 3 mg was added to the obtained residue, and the reaction liquor was stirred at 120°C for two hours. The reaction liquor was diluted with ethyl acetate, and after washing with water, it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was refined by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.19 (3H, s), 3.97 (3H, s), 6.94-7.00 (1H, m), 6.99 (1/2H, brs), 7.00-7.14 (4H, m), 7.27-7.33 (1H, m), 7.30 (1/2H, brs), 7.40 (1/2H, brs), 7.46 (1H, d, J = 2.4 Hz), 7.65 (1/2H, brs), 7.98 (1H, d, J = 8.8 Hz), 8.42 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 480 (M+H).

#### Example 204

##### 5-(2-chloro-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

###### Step 1

##### Synthesis of 4-(2-chlorophenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-chlorophenol, the title compound was obtained by the same process as in Example 196 (Step 4)-(Step 5), a process based on these or a combination of these with a normal procedure.

###### Step 2

##### Production of 5-(2-chloro-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To methanol 1 ml solution of 4-(2-chlorophenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 35 mg obtained in (Step 1) were added aniline and 1 M methanol solution 0.26 ml of pyridine-2-carboxaldehyde (1 : 1), and the reaction liquor was stirred at 60°C overnight. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous sodium sulphate.

The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.17 (3H, s), 6.92 (1H, d, J = 8.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.22 (1H, t, J = 8.0 Hz), 7.26-7.66 (4H, m), 7.66-7.80 (1H, brs), 7.90-8.08 (2H, m), 8.29 (1H, d, J = 8.0 Hz), 8.31 (1H, d, J = 2.4 Hz), 8.72 (1H, s).

ESI-MS (m/e): 493 (M+H).

#### Example 205

##### 5-(2-chloro-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.5 ml solution of 4-(2-chloro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine 38 mg obtained in Example 204 (Step 1) were added methylpyrazine-2-imidate (Pyrazine-2-carboximide methyl ester) 15 mg and methanesulfonic acid 0.0065 ml, and the reaction liquor was stirred at 120°C for 20 minutes. The reaction liquor was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. By eliminating the solvent under reduced pressure, the title compound was obtained as yellow colored solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.20 (3H, s), 6.97 (1H, d, J = 7.8 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.26 (1H, t, J = 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.48 (1H, dd, J = 8.6, 2.3 Hz), 7.60-7.82 (2H, m), 8.02 (1H, d, J = 8.6 Hz), 8.35 (1H, d, J = 2.3 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 494 (M+H).

#### Example 206

##### 5-(2-trifluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-trifluoromethyl phenol, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.17 (3H, s), 6.93-6.98 (1H, m), 7.21 (1H, t, J = 7.4 Hz), 7.40-7.81 (6H, m), 7.97-8.05 (2H, m), 8.24-8.39 (2H, m), 8.73-8.87 (1H, m).

ESI-MS (m/e): 527 (M+H).

#### Example 207

##### 5-(2-trifluoromethyl-phenoxy)-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

zimidazole

Using

4-(2-trifluoromethyl-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 206 and methylpyrazine-2-imidate, the title compound was obtained as yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.17 (3H, s), 6.97 (1H, d, J = 7.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 7.46 (1H, dd, J = 8.6, 2.3 Hz), 7.54 (1H, t, J = 7.8 Hz), 7.44-7.60 (1H, m), 7.65 (1H, d, J = 7.8 Hz), 7.84-7.86 (1H, m), 8.01 (1H, d, J = 8.6 Hz), 8.31 (1H, d, J = 2.3 Hz), 8.73 (1H, d, J = 2.3 Hz), 8.80 (1H, d, J = 2.3 Hz), 9.50 (1H, s)

ESI-MS (m/e): 528 (M+H).

**Example 208**5-(3-trifluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 3-trifluoromethyl phenol, the title compound was obtained as a white solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.20 (3H, s), 7.00-7.15 (2H, m), 7.37 (1H, d, J = 7.8 Hz), 7.45-7.55 (3H, m), 7.66 (1H, d, J = 10.0 Hz), 7.76 (1H, brs), 7.99-8.04 (2H, m), 8.30-8.35 (2H, m), 8.77 (1H, d, J = 2.7 Hz)

ESI-MS (m/e): 527 (M+H).

**Example 209**5-(4-trifluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 4-trifluoromethyl phenol, the title compound was obtained as a white solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.20 (3H, s), 6.98 (2H, d, J = 8.6 Hz), 7.46-7.77 (4H, m), 7.60 (2H, d, J = 8.6 Hz), 8.00-8.04 (2H, m), 8.31 (1H, d, J = 3.1 Hz), 8.34 (1H, d, J = 8.2 Hz), 8.78 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 527 (M+H).

**Example 210**5-(2-difluoromethyl-phenoxy)-2-pyridine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

zimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-difluoromethyl phenol, the title compound was obtained as a brown solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.17 (3H, s), 6.70 (1H, t, J = 55.2 Hz), 6.87 (1H, d, J = 7.4 Hz), 7.18 (1H, t, J = 7.4 Hz), 7.40-7.46 (2H, m), 7.50-7.59 (3H, m), 7.59-7.82 (1H, m), 7.98-8.04 (2 H, m), 8.27-8.35 (2H, m), 8.76 (1H, brs)

ESI-MS (m/e): 509 (M+H).

**Example 211**5-(2-fluoropyridine-3-yloxy)-6-(6-methanesulphonyl  
pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-fluoro-pyridin-3-ol synthesised by a process described in Journal of Medicinal Chemistry, 1999, vol. 42, issue 12, pp.2251-2259, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.21 (3H, s), 7.11-7.17 (1H, m), 7.22 (1/2H, s), 7.29-7.36 (2H, m), 7.29-7.36 (1/2H, m), 7.40-7.43 (1H, s), 7.53 (1/2H, s), 7.72 (1/2H, s), 7.88-7.93 (1H, m), 7.93-7.96 (1H, m), 7.99-8.03 (1H, m), 8.37-8.41 (2H, m), 8.65-8.67 (1H, m), 10.78 (1/2H, brs), 10.82 (1/2H, brs).

ESI-MS (m/e): 478 (M+H).

**Example 212**5-(2-fluoropyridine-3-yloxy)-6-(6-methanesulphonyl pyridine-3-yloxy)-2-pyrazine-2-yl  
-1H-benzimidazole

Using 4-(2-fluoro-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene -1,2-diamine obtained in Example 211 and pyrazine-2-carboxylic acid, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.21 (3H, s), 7.14-7.19 (1H, m), 7.23 (1/2H, s), 7.26-7.40 (2H, m), 7.46 (1/2H, s), 7.54 (1/2H, s), 7.56 (1/2H, s), 7.96-8.00 (1H, m), 8.03 (1H, dd, J = 8.6, 3.9 Hz), 8.41 (1H, dd, J = 2.7, 1.6 Hz), 8.62 (1H, ddd, J = 4.7, 2.7, 1.6 Hz), 8.69-8.71 (1H, m), 9.62 (1H, dd, J = 6.3, 1.6 Hz), 10.48 (1/2H, brs), 10.56 (1/2H, brs).

ESI-MS (m/e): 479 (M+H).

**Example 213**

5-(2-fluoropyridine-3-yloxy)-2-(1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1H-pyrazole-3-carboxaldehyde and 4-(2-fluoro-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 211, the title compound was obtained as a colourless solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.21 (3H, s), 7.08 (1H, d, J = 2.3 Hz), 7.09-7.19 (1H, m), 7.19-7.49 (4H, m), 7.71 (1H, d, J = 2.3 Hz), 7.88-7.96 (1H, m), 7.97-8.03 (1H, m), 8.36 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 467 (M+H).

**Example 214**

5-(2-fluoropyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-fluoro-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 211, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.20 (3H, s), 4.00 (3H, s), 7.00 (1H, d, J = 2.4 Hz), 7.10-7.16 (1H, m), 7.19 (1/2H, brs), 7.26-7.33 (2H, m), 7.35 (1/2H, brs), 7.48 (1H, d, J = 2.4 Hz), 7.52 (1/2H, brs), 7.67 (1/2H, brs), 7.91-7.94 (1H, m), 8.00 (1H, d, J = 8.6 Hz), 8.37 (1H, d, J = 2.5 Hz), 10.13 (1H, brs).

ESI-MS (m/e): 481 (M+H).

**Example 215**

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 2-difluoromethoxy-pyridine-3-ol obtained in Reference Example 2, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 3.22 (3H, s), 7.19-7.27 (1H, m), 7.29-7.86 (6H, m), 7.95-8.07 (3H, m), 8.33-8.35 (1H, m), 8.45-8.48 (1H, m), 8.77 (1H, s).

ESI-MS (m/e): 526 (M+H).

**Example 216**

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using methylpyrazine-2-imidate and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 215, the title

compound was obtained as a colourless solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 3.20 (3H, s), 7.21 (1H, dd, J = 7-8, 4.9 Hz), 7.30-7.90 (4H, m), 7.62 (1H, t, J = 72.6 Hz), 7.94 (1H, d, J = 8.8 Hz), 7.97 (1H, d, J = 4.8 Hz), 8.45 (1H, d, J = 2.7 Hz), 8.77-8.83 (2H, m), 9.48 (1H, s)

ESI-MS (m/e): 527[M+H].

#### Example 217

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 215, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 3.22 (3H, s), 4.00 (3H, s), 6.88 (1H, d, J = 2.2 Hz), 7.17-7.82 (6H, m), 7.90-7.99 (3H, m), 8.42-8.45 (1H, m)

ESI-MS (m/e): 529 (M+H).

#### Example 218

5-(2-cyanopyridine-3-yloxy)-6-(6-methanesulphonyl pyridine-3-yloxy)-2- pyridine-2-yl -1H-benzimidazole

##### Step 1

Synthesis of 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro -5-(1-oxy-pyridine-3-yloxy)-phenylamine

Using 5-fluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 196 (Step 3) and 1-oxy-pyridin-3-ol, the title compound was obtained by the same process as in Example 196 (Step 4), a process based on this or a combination of these with a normal procedure.

##### Step 2

Synthesis of 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-5-(2 -cyano-pyridine-3 -yloxy)-phenylamine

To acetonitrile 6 ml solution of 216 mg of 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-5-(1-oxy-pyridine-3-yloxy)-phenylamine were added trimethylsilyl nitrile 0.90 ml and triethylamine 0.90 ml, and thereafter the reaction liquor was stirred while heating under reflux overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, 1,1,1,3,3,3-hexamethyldisilazane was added, and the reaction liquor was stirred while heating under reflux for one hour. The reaction liquor was purified by silica gel column

chromatography (eluent: chloroform/methanol = 30/1), and the title compound was obtained.

### Step 3

#### Production of 5-(2-cyanopyridine-3-yloxy)-6-(6-methanesulphonyl pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 4-(6-methanesulphonyl-pyridine-3-yloxy)-2-nitro-5-(2-cyano-pyridine-3-yloxy)-phenylamine, the title compound was obtained as a white solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.22 (3/2H, s), 3.23 (3/2H, s), 7.18-7.23 (2H, m), 7.40-7.48 (2H, m), 7.50 (1H, s), 7.76-7.78 (1H, m), 7.91-7.95 (1H, m), 8.03-8.06 (1H, m), 8.20-8.23 (1H, m), 8.37-8.44 (2H, m), 8.58-8.67 (1H, m), 11.04 (1H, brs).

ESI-MS (m/e): 485 (M+H).

### Example 219

#### 5-(2-cyanopyridine-3-yloxy)-6-(6-methanesulphonyl pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-cyanopyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 218 (Step 3) and pyrazine-2-carboxylic acid, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.23 (3/2H, s), 3.24 (3/2H, s), 7.21-7.26 (2H, m), 7.42-7.48 (1H, m), 7.55 (1H, d, J = 1.2 Hz), 7.80 (1/2H, s), 7.8.2 (1/2H, s), 8.04 (1/2H, s), 8.06 (1/2H, s), 8.19-8.21 (1H, m), 8.41 (1H, dd, J = 4.5, 1.2 Hz), 8.65 (1H, dd, J = 3.9, 2.3 Hz), 8.73 (1H, d, J = 2.3 Hz), 9.65 (1H, d, J = 1.2 Hz), 10.99 (1H, brs).

ESI-MS (m/e): 486 (M+H).

### Example 220

#### 5-(2-cyanopyridine-3-yloxy)-2-(1H-pyrazol-3-yl)-6-(6-methanesulfonyl pyridine-3-yloxy)-1H-benzimidazole

Using 4-(2-cyanopyridine-3-yloxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 218 (Step 3) and 1H-pyrazole-3-carboxaldehyde, the title compound was obtained as a colourless solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.22 (3H, s), 7.12 (1H, d, J = 2.3 Hz), 7.17-7.25 (2H, m), 7.40-7.48 (2H, m), 7.71-7.74 (1H, m), 7.72 (1H, d, J = 2.3 Hz), 8.00-8.03 (1H, m), 8.17-8.21 (1H, m), 8.38-8.41 (1H, m).

ESI-MS (m/e): 474 (M+H).

**Example 221****5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole****Step 1****Synthesis of 3-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-phenylamine**

To dimethylformamide 150 ml solution of (3-fluoro-4-hydroxy-phenyl)-carbamic acid tert-butyl ester 10.0 g obtained in Example 196 (Step 1) were added 5-chloro-2-ethane sulfonyl-pyridine 10.9 g and cesium carbonate 21.6 g, and the reaction liquor was stirred at 100°C for three hours. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/9), and crude product was obtained. The obtained crude product was dissolved in 4 N hydrochloric acid-dioxane and was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was diluted with chloroform and was washed using water, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/9), and the title compound was obtained.

**Step 2****Synthesis of 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine**

To 3-fluoro-4-(6-ethane sulfonyl-pyridine-3-yloxy)-phenylamine 10.5 g dissolved in trifluoroacetic acid 100 ml solution was added potassium nitrate 3.8 g, and the reaction liquor was stirred at room temperature for one hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2), and the title compound was obtained.

**Step 3****Production of 5-(2-cyano-phenoxy)-2-pyridine-2-yl-6-(6-ethane sulfonyl-pyridine-3-yloxy)-1H-benzimidazole**

To 3 ml solution of N-methylpyrrolidinone of 5-fluoro-4-(6-ethane sulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine 150 mg were added 2-hydroxy-benzonitrile 60 mg and potassium carbonate 70 mg, and the reaction liquor was stirred at 90°C for five hours. Water was added to the reaction liquor, and thereafter, crude product was obtained by recovering the precipitate by



filtration. To methanol 5 ml solution of the obtained crude product, expanded Raney nickel catalyst 10 mg and hydrazine • monohydrate 0.12 ml were added, and the reaction liquor was stirred for one hour. The catalyst was eliminated by filtration, thereafter the solvent was eliminated by distillation under reduced pressure, and crude product 160 mg was obtained. To methanol 3 ml solution of the obtained crude product 35 mg, 1M methanol solution 0.20 ml of aniline and pyridine-2-carboxaldehyde (1 : 1) was added, and the reaction liquor was stirred at 80°C overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was refined by preparative thin layer chromatography (Kieselgel™60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.27 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 6.91 (1H, d, J = 7.8 Hz), 7.19 (1H, t, J = 7.8 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.50-7.60 (2H, m), 7.60-7.90 (3H, m), 7.99-8.04 (2H, m), 8.26 (1H, s), 8.34 (1H, d, J = 7.8 Hz), 8.77 (1H, s).

ESI-MS (m/e): 498 (M+H).

#### Example 222

##### 5-(2-cyano-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 4-(2-cyano-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 221 (Step 3) and methylpyrazine-2-imidate, the title compound was obtained as a brown solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.28 (3H, t, J = 7.6 Hz), 3.38 (2H, q, J = 7.6 Hz), 6.94 (1H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.45 (1H, dd, J = 8.6, 2.7 Hz), 7.58 (1H, td, J = 7.6, 1.8 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.68-7.90 (2H, m), 8.03 (1H, d, J = 8.6 Hz), 8.28 (1H, d, J = 2.7 Hz), 8.75 (1H, d, J = 2.0 Hz), 8.82 (1H, dd, J = 2.0, 1.2 Hz), 9.54 (1H, 1.2 Hz = d).

ESI-MS (m/e): 499 (M+H).

#### Example 223

##### 5-(2-fluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-fluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.18-1.24 (3H, m), 3.02-3.41 (2H, m), 6.97-7.40 (5H, m), 7.47-7.77 (3H, m), 7.96-8.04 (2H, m), 8.30 (1H, d, J = 7.8 Hz), 8.39-8.42 (1H, m), 8.73-8.78 (1H, m).

ESI-MS (m/e): 491 (M+H).

#### Example 224

5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 4-(2-fluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 223 and methylpyrazine-2-imidate, the title compound was obtained as a brown solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.22 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 7.52 (1H, dd, J = 3.1, 8.6 Hz), 7.00-7.80 (6H, m), 8.04 (1H, d, J = 8.6 Hz), 8.42 (1H, d, J = 3.1 Hz), 8.72 (1H, s), 8.79 (1H, s), 9.49 (1H, s).

ESI-MS (m/e): 492 (M+H).

**Example 225**5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1H-pyrazole-3-carboxaldehyde and 4-(2-fluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 223, the title compound was obtained as a straw-coloured solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.22 (3H, t, J = 7.4 Hz), 3.30-3.42 (2H, m), 6.88 (1H, d, J = 1.6 Hz), 6.99-7.04 (1H, m), 7.07-7.20 (3H, m), 7.22-7.43 (1H, m), 7.49 (1H, dd, J = 7.8, 3.1 Hz), 7.56-7.68 (1H, m), 7.83 (1H, d, J = 1.6 Hz), 8.02 (1H, d, J = 7.8 Hz), 8.39 (1H, d, J = 3.1 Hz).

ESI-MS (m/e): 480 (M+H).

**Example 226**5-(2,3-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,3-difluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.69-6.75 (1H, m), 6.91-7.02 (2H, m), 7.20 (1/2H, s), 7.27-7.34 (1H, m), 7.37-7.47 (1H, m), 7.41 (1/2H, s), 7.53 (1/2H, s), 7.72 (1/2H, s), 7.87-7.92 (1H, m), 8.00 (1/2H, d, J = 8.7 Hz), 8.01 (1/2H, d, J = 8.7 Hz), 8.36-8.41 (1H, m), 8.42 (1H, d, J = 2.7 Hz), 8.63-8.67 (1H, m), 10.75 (1/2H, brs), 10.80 (1/2H, brs).

ESI-MS (m/e): 509 (M+H).

**Example 227**5-(2,3-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

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Using 4-(2,3-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 226 and pyrazine-2-carboxylic acid, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 6.72-6.78 (1H, m), 6.92-7.05 (2H, m), 7.22 (1/2H, s), 7.33 (1/2H, dd, J = 8.8, 2.7 Hz), 7.34 (1/2H, dd, J = 8.8, 2.7 Hz), 7.45 (1/2H, s), 7.53 (1/2H, s), 7.75 (1/2H, s), 8.01 (1/2H, d, J = 8.8 Hz), 8.02 (1/2H, d, J = 8.8 Hz), 8.43 (1H, d, J = 2.7 Hz), 8.60 (1/2H, dd, J = 2.5, 1.6 Hz), 8.62 (1/2H, dd, J = 2.5, 1.6 Hz), 8.69 (1/2H, d, J = 2.5 Hz), 8.70 (1/2H, d, J = 2.5 Hz), 9.61 (1/2H, d, J = 1.6 Hz), 9.63 (1/2H, d, J = 1.6 Hz), 10.52 (1/2H, brs), 10.62 (1/2H, brs).

ESI-MS (m/e): 510 (M+H).

#### Example 228

5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2,3-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 226, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (1H, q, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.97 (2H, s), 3.98 (1H, s), 6.65-6.75 (1/3H, m), 6.87 (1/2H, brs), 6.89-7.01 (3H, m), 7.10-7.19 (1H, m), 7.26-7.38 (1H, m), 7.30 (1/2H, s), 7.45 (2/3H, d, J = 2.3 Hz), 7.47 (1/3H, d, J = 2.3 Hz), 7.50-7.53 (1/6H, m), 7.62-7.67 (2H, m), 7.95-8.05 (1H, m), 8.39 (1/3H, d, J = 2.5 Hz), 8.54 (2/3H, d, J = 2.5 Hz), 10.00-10.25 (1H, m).

ESI-MS (m/e): 512 (M+H).

#### Example 229

5-(2,4-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,4-difluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (1H, q, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 6.81-6.95 (2H, m), 6.95-7.05 (1H, m), 7.06 (1/2H, s), 7.33 (1/2H, s), 7.32 (1/2H, dd, J = 8.6, 2.7 Hz), 7.34 (1/2H, dd, J = 8.6, 2.7 Hz), 7.37-7.41 (1H, m), 7.40 (1/2H, s), 7.70 (1/2H, s), 7.86-7.91 (1H, m), 8.00 (1/2H, d, J = 8.6 Hz), 8.01 (1/2H, d, J = 8.6 Hz), 8.34-8.39 (1H, m), 8.46 (1H, d, J

= 2.7 Hz), 8.62-8.67 (1H, m), 10.67 (1/2H, brs), 10.76 (1/2H, brs).

ESI-MS (m/e): 509 (M+H).

#### Example 230

##### 5-(2,4-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2,4-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 229, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 6.82-6.95 (2H, m), 6.98-7.05 (1H, m), 7.08 (1/2H, s), 7.34 (1/2H, dd, J = 8.6, 2.7 Hz), 7.35 (1/2H, dd, J = 8.6, 2.7 Hz), 7.38 (1/2H, s), 7.44 (1/2H, s), 7.74 (1/2H, s), 8.02 (1/2H, d, J = 8.6 Hz), 8.03 (1/2H, d, J = 8.6 Hz), 8.46 (1/2H, d, J = 2.7 Hz), 8.47 (1/2H, d, J = 2.7 Hz), 8.58 (1/2H, dd, J = 2.7, 1.6 Hz), 8.60 (1/2H, dd, J = 2.7, 1.6 Hz), 8.67 (1/2H, d, J = 2.7 Hz), 8.68 (1/2H, d, J = 2.7 Hz), 9.59 (1/2H, d, J = 1.6 Hz), 9.61 (1/2H, d, J = 1.6 Hz), 10.54 (1/2H, brs), 10.69 (1/2H, brs).

ESI-MS (m/e): 510 (M+H).

#### Example 231

##### 5-(2,4-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2,4-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 229, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.28 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 3.98 (3H, s), 6.78-6.85 (1H, m), 6.85-6.93 (1H, m), 6.93-6.98 (1H, m), 6.93-6.98 (1/2H, m), 6.99 (1H, d, J = 2.3 Hz), 7.02 (1/2H, brs), 7.27-7.34 (1H, m), 7.36 (1/2H, brs), 7.46 (1H, d, J = 2.3 Hz), 7.64 (1/2H, brs), 7.99 (1H, d, J = 8.6 Hz), 8.43 (1H, d, J = 2.7 Hz), 10.19 (1/2H, brs), 10.29 (1/2H, brs).

ESI-MS (m/e): 512 (M+H).

#### Example 232

##### 5-(2,5-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,5-difluoro-phenol, the title compound was obtained as a white solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.23 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.76-6.89 (2H, m), 7.15-7.24 (1H, m), 7.49-7.55 (3H, m), 7.71 (1H, s), 8.01 (1H, td, J = 7.4, 2.3 Hz), 8.04 (1H, d, J = 7.4 Hz), 8.32 (1H, d, J = 7.4 Hz), 8.40 (1H, d, J = 2.3 Hz), 8.77 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 509 (M+H).

#### Example 233

##### 5-(2,5-difluoro-phenoxy)-2-pyridine-1-oxide-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

To chloroform 1.5 ml solution of 5-(2,5-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole 7.5 mg obtained in Example 232 was added m-chloroperbenzoic acid 7.5 mg, and thereafter the reaction liquor was stirred at 45°C for one hour. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.23 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.78-6.90 (2H, m), 7.20 (1H, td, J = 9.8, 5.1 Hz), 7.52 (1H, dd, J = 6.6, 3.1 Hz), 7.56 (1H, s), 7.62 (1H, t, J = 8.2 Hz), 7.73 (1H, t, J = 8.2 Hz), 7.78 (1H, s), 8.04 (1H, d, J = 8.2 Hz), 8.41 (1H, d, J = 3.1 Hz), 8.51 (1H, d, J = 6.6 Hz), 8.64 (1H, d, J = 8.2 Hz).

ESI-MS (m/e): 525 (M+H).

#### Example 234

##### 5-(2,5-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using methylpyrazine-2-imidate and 4-(2,5-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 232, the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 6.9 Hz), 3.38 (2H, q, J = 6.9 Hz), 6.77-6.91 (2H, m), 7.17-7.24 (1H, m), 7.51 (1H, s), 7.52 (1H, dd, J = 7.4, 4.3 Hz), 7.74 (1H, s), 8.04 (1H, d, J = 7.4 Hz), 8.41 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 4.3 Hz), 8.80 (1H, dd, J = 2.3, 1.8 Hz), 9.51 (1H, d, J = 1.8 Hz).

ESI-MS (m/e): 510 (M+H).

#### Example 235

5-(2,6-difluoro-phenoxy)-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2,6-difluoro-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 6.68-6.75 (1/2H, m), 6.90-7.00 (2H, m), 7.12-7.26 (1H, m), 7.27-7.53 (3H, m), 7.68-7.72 (1/2H, m), 7.84-7.92 (1H, m), 7.98-8.04 (1H, m), 8.31-8.39 (1H, m), 8.41 (1/2H, d, J = 2.3 Hz), 8.56 (1/2H, d, J = 2.3 Hz), 8.57-8.63 (1H, m), 10.59-10.88 (1H, m).

ESI-MS (m/e): 509 (M+H).

**Example 236**

5-(2,6-difluoro-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2,6-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 235, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (1/2H, q, J = 7.4 Hz), 3.39, (1H, q, J = 7.4 Hz), 3.40 (1/2H, q, J = 7.4 Hz), 6.73-6.78 (1/2H, m), 6.93-7.04 (2H, m), 6.93-7.04 (1/2H, m), 7.14-7.20 (1/2H, m), 7.22 (1/4H, s), 7.31-7.42 (1H, m), 7.44 (1/4H, s), 7.45 (1/4H, s), 7.53 (1/4H, s), 7.74 (1/4H, s), 7.75 (1/4H, s), 8.00-8.05 (1H, m), 8.43 (1/2H, d, J = 2.7 Hz), 8.56 (1/4H, dd, J = 2.5, 1.6 Hz), 8.57 (1/2H, d, J = 2.7 Hz), 8.59 (1/4H, dd, J = 2.5, 1.6 Hz), 8.60 (1/4H, dd, J = 2.5, 1.6 Hz), 8.61 (1/4H, dd, J = 2.5, 1.6 Hz), 8.66 (1/4H, d, J = 2.5 Hz), 8.67 (1/4H, d, J = 2.5 Hz), 8.68 (1/4H, d, J = 2.5 Hz), 8.69 (1/4H, d, J = 2.5 Hz), 9.56 (1/4H, d, J = 1.6 Hz), 9.60 (1/4H, d, J = 1.6 Hz), 9.61 (1/4H, d, J = 1.6 Hz), 9.63 (1/4H, d, J = 1.6 Hz), 10.36 (1/4H, brs), 10.48 (1/4H, brs), 10.51 (1/4H, brs), 10.57 (1/4H, brs)

ESI-MS (m/e): 510 (M+H).

**Example 237**

5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2,6-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 235, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 3.96 (3H, s), 6.87 (1/2H, brs), 6.93-7.00 (3H, m), 7.10-7.17 (1H, m), 7.18 (1/2H, s), 7.30 (1/2H, s), 7.32-7.40 (1H, m), 7.34 (1H, d, J = 2.5 Hz), 7.63 (1/2H, brs), 7.98-8.03 (1H, m), 8.54 (1H, d, J = 2.7 Hz), 10.18 (1/2H, brs), 10.35 (1/2H, brs).

ESI-MS (m/e): 512 (M+H).

#### Example 238

5-(2-trifluoromethoxy-phenoxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-trifluoromethoxy-phenol, the title compound was obtained as a colourless solid by the same process as in Example 196 (Step 4), (Step 5) and Example 205, a process based on these or a combination of these successively with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.27 (3H, t, J = 7.4 Hz), 3.36 and 3.37 (total 2H, each q, J = 7.4 Hz), 6.95-7.00 (1H, m), 7.12-7.46 (5H, m), 7.50 and 7.76 (total 1H, each s), 7.98 and 8.00 (total 1H, each d, J = 8.8 Hz), 8.41 (1H, d, J = 2.7 Hz), 8.59-8.62 (1H, m), 8.68 (1H, d, J = 2.4 Hz), 9.61 and 9.63 (total 1H, each d, J = 1.6 Hz).

ESI-MS (m/e): 558 (M+H).

#### Example 239

5-(2-fluoropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-fluoro-pyridin-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 7.11-7.16 (1H, m), 7.24 (1/2H, s), 7.26-7.35 (2H, m), 7.41-7.45 (1H, m), 7.43 (1/2H, s), 7.55 (1/2H, s), 7.72 (1/2H, s), 7.88-7.94 (2H, m), 7.99-8.03 (1H, m), 8.38-8.41 (2H, m), 8.65-8.67 (1H, m), 10.94 (1/2H, brs), 10.98 (1/2H, brs)

ESI-MS (m/e): 492 (M+H).

#### Example 240

5-(2-fluoropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2-fluoropyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 239, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a

combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30 (3H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 7.13-7.24 (1H, m), 7.24 (1/2H, s), 7.26-7.39 (2H, m), 7.47 (1/2H, s), 7.56 (1/2H, s), 7.77 (1/2H, s), 7.95-8.05 (2H, m), 8.40 (1H, d, J = 2.3 Hz), 7.62 (1/2H, dd, J = 2.4, 1.6 Hz), 8.63 (1/2H, dd, J = 2.4, 1.6 Hz), 8.70 (1/2H, d, J = 2.4 Hz), 8.71 (1/2H, d, J = 2.4 Hz), 9.62 (1/2H, d, J = 1.6 Hz), 9.63 (1/2H, d, J = 1.6 Hz), 10.45 (1/2H, brs), 10.51 (1/2H, brs).

ESI-MS (m/e): 493 (M+H).

#### Example 241

5-(2-fluoropyridine-3-yloxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1H-pyrazole-3-carboxaldehyde and 4-(2-fluoropyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 239, the title compound was obtained as a colourless solid by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.07 (1H, d, J = 2.7 Hz), 7.08-7.13 (1H, m), 7.20 (1/2H, brs), 7.24-7.30 (2H, m), 7.34 (1/2H, brs), 7.52 (1/2H, brs), 7.65 (1/2H, brs), 7.71 (1H, d, J = 2.7 Hz), 7.88-7.92 (1H, m), 7.99 (1H, d, J = 8.6 Hz), 8.33 (1H, d, J = 2.7 Hz)

ESI-MS (m/e): 481 (M+H).

#### Example 242

5-(2-chloropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2- pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-chloro-pyridin-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 7.14-7.20 (2H, m), 7.28 (1/2H, s), 7.20-7.31 (1H, m), 7.40-7.46 (1H, m), 7.46 (1/2H, s), 7.60 (1/2H, s), 7.76 (1/2H, s), 7.88-7.93 (1H, m), 8.00 (1/2H, d, J = 8.6 Hz), 8.01 (1/2H, d, J = 8.6 Hz), 8.11-8.16 (1H, m), 8.31-8.35 (1H, m), 8.38-8.42 (1H, m), 8.64-8.68 (1H, m), 10.82-10.95 (1H, m).

ESI-MS (m/e): 508 (M+H).

#### Example 243

5-(2-chloropyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2-chloropyridine-3-yloxy)-5-(6-ethane



sulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 242, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.18-7.24 (2H, m), 7.30 (1/2H, s), 7.31 (1/2H, dd, J = 8.6, 2.7 Hz), 7.32 (1/2H, dd, J = 8.6, 2.7 Hz), 7.51 (1/2H, s), 7.61 (1/2H, s), 7.81 (1/2H, s), 8.02 (1/2H, d, J = 8.6 Hz), 8.04 (1/2H, d, J = 8.6 Hz), 8.15-8.20 (1H, m), 8.35 (1/2H, d, J = 2.7 Hz), 8.36 (1/2H, d, J = 2.7 Hz), 8.63 (1/2H, dd, J = 2.3, 1.6 Hz), 8.64 (1/2H, dd, J = 2.3, 1.6 Hz), 8.72 (1/2H, d, J = 2.3 Hz), 8.73 (1/2H, d, J = 2.3 Hz), 9.64 (1/2H, d, J = 1.6 Hz), 9.65 (1/2H, d, J = 1.6 Hz), 10.60 (1/2H, brs), 10.68 (1/2H, brs).

ESI-MS (m/e): 509 (M+H).

#### Example 244

##### 5-(2-chloropyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-chloropyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 242, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 4.01 (3H, s), 7.01 (1H, d, J = 2.3 Hz), 7.12-7.17 (2H, m), 7.26 (1H, dd, J = 8.8, 2.7 Hz), 7.39 (1/2H, brs), 7.48 (1/2H, brs), 7.49 (1H, d, J = 2.3 Hz), 7.58 (1/2H, brs), 7.69 (1/2H, brs), 7.99 (1H, d, J = 8.8 Hz), 8.10-8.15 (1H, m), 8.31 (1H, d, J = 2.7 Hz), 10.28 (1H, brs).

ESI-MS (m/e): 511 (M+H).

#### Example 245

##### 5-(2-cyanopyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 1-oxy-pyridin-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 218, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.12-7.26 (3H, m), 7.38-7.45 (2H, m), 7.45 (1/2H, s), 7.46 (1/2H, s), 7.75 (1H, s), 7.89-7.94 (1H, m), 7.99-8.05 (1H, m), 8.22-8.26 (1H, m), 8.39-8.43 (1H, m), 8.67-8.70 (1H, m), 10.88 (1H, brs).

ESI-MS (m/e): 499 (M+H).

#### Example 246

##### 5-(2-cyanopyridine-3-yloxy)-6-(6-ethanesulfonyl pyridine-3-yloxy)-2-pyrazine-

2-yl-1H-benzimidazole

Using pyrazine-2-carboxylic acid and 4-(2-cyanopyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 245, the title compound was obtained as a colourless solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.35 (3/2H, t, J = 7.4 Hz), 1.37 (3/2H, t, J = 7.4 Hz), 3.38 (1H, q, J = 7.4 Hz), 3.39 (1H, q, J = 7.4 Hz), 7.19-7.26 (2H, m), 7.42-7.47 (1H, m), 7.53 (1/2H, s), 7.54 (1/2H, s), 7.80 (1/2H, s), 7.81 (1/2H, s), 8.04 (1/2H, d, J = 8.6 Hz), 8.05 (1/2H, d, J = 8.6 Hz), 8.22-8.25 (1H, m), 8.40-8.43 (1H, m), 8.64-8.66 (1H, m), 8.73 (1H, d, J = 2.5 Hz), 9.65 (1H, d, J = 1.5 Hz), 10.87 (1/2H, brs), 10.90 (1/2H, brs)

ESI-MS (m/e): 500 (M-H).

**Example 247**5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 2-difluoromethoxy-pyridine-3-ol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.10 (3H, t, J = 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 7.18-7.25 (1H, m), 7.31-7.87 (6H, m), 7.94-8.07 (3H, Lm), 8.32-8.36 (1H, m), 8.46-8.49 (1H, m), 8.77 (1H, s).

ESI-MS (m/e): 540 (M+H).

**Example 248**5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

Using methylpyrazine-2-imidate and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 247, the title compound was obtained as a colourless solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 7.07-7.11 (1H, m), 7.17 and 7.76 (total 1H, each s), 7.29-7.34 (2H, m), 7.37 (1H, t, J = 72.8 Hz), 7.46 (1H, s), 7.96-8.03 (2H, m), 8.43 (1H, s), 8.60 and 8.62 (total 1H, each s), 8.69 (1H, s), 9.60 and 9.63 (total 1H, each d, J = 1.5 Hz).

ESI-MS (m/e): 541 (M+H).

**Example 249**5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(6-ethane

sulfonyl-pyridine-3-yloxy)-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole

Using 1-methyl-1H-pyrazole-3-carboxylic acid and 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 247, the title compound was obtained as a colourless solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.10 (3H, t, J = 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 4.00 (3H, s), 6.88 (1H, d, J = 2.3 Hz), 7.19 (1H, brs), 7.26-7.75 (4H, m), 7.63 (1H, t, J = 72.4 Hz), 7.90-7.99 (3H, m), 8.45 (1H, d, J = 2.7 Hz).

ESI-MS (m/e): 543 (M+H).

**Example 250**6-benzyloxy-5-(2-fluorophenoxy)-2-pyrazine-2-yl-1H-benzimidazole**Step 1**Synthesis of 4-benzyloxy-3-fluoroaniline

To methanol 60 ml solution of 4-benzyloxy-3-fluoro nitrobenzene 4.94 g, 2.91 ml hydrazine monohydrate and about 1 g expanded Raney nickel catalyst were added, and the reaction liquor was stirred at room temperature for two hours. By eliminating the solvent under reduced pressure after eliminating the catalyst by filtration with celite, the title compound was obtained as a yellow oily substance.

**Step 2**Synthesis of N-(4-benzyloxy-3-fluorophenyl) pyrazine carboxamide

To pyridine 60 ml solution of 4-benzyloxy-3-fluoroaniline 4.13 g, pyrazine-2-carboxylic acid 2.59 g and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 4.73 g were added, and the reaction liquor was stirred at room temperature overnight. Pyridine was eliminated by distillation under reduced pressure, and thereafter, water was added. By recovering the formed precipitate by filtration, the title compound was obtained as a brown solid.

**Step 3**Synthesis of N-(4-benzyloxy-5-fluoro-2-nitrophenyl) pyrazine carboxamide

To chloroform 40 ml suspension of N-(4-benzyloxy-3-fluorophenyl) pyrazine carboxamide 5.80 g, trifluoroacetic acid 40 ml and potassium nitrate 1.99 g were added under ice cooling, and the reaction liquor was stirred at room temperature overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, saturated aqueous sodium bicarbonate was added. The formed precipitate was recovered by filtration and thereafter, washed using water. By washing the obtained solid with mixed solvent of ethyl acetate and hexane, the title compound was obtained as yellow solid.

**Step 4**Synthesis of N-(4-benzyloxy-5-(2-fluorophenoxy)-2-nitrophenyl) pyrazine carboxamide

To dimethylformamide 16 ml solution of N-(4-benzyloxy-5-fluoro-2-nitrophenyl) pyrazine carboxamide 2.14 g, 2-fluorophenol 0.54 ml and potassium carbonate 2.53 g were added, and the reaction liquor was stirred at 90°C for five hours, and thereafter, water was added. By recovering the formed precipitate by filtration, the title compound was obtained as yellow solid.

**Step 5**Production of 5-benzyloxy-6-(2-fluorophenoxy)-2-pyrazine-2-yl-1H-benzimidazole

To dimethylformamide 16 ml suspension of N-(4-benzyloxy-5-(2-fluorophenoxy)-2-nitrophenyl) pyrazine carboxamide 1.52 g, tin chloride (II) dihydrate 3.72 g was added, and the reaction liquor was stirred at 80°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and, by washing the obtained residue with mixed solvent of ethyl acetate and hexane, the title compound was obtained as yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 5.15 and 5.17 (total 2H, each s), 6.78-6.93 (1H, m), 7.06-7.40 (9H, m), 7.54 and 7.57 (total 1H, each s), 8.73 and 8.74 (total 1H, each s), 8.76-8.79 (1H, m), 9.43 and 9.44 (total 1H, each d, J = 1.6 Hz).

ESI-MS (m/e): 413 (M+H).

**Example 251**5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(2-cyano-pyrimidine-5-yloxy)-1H-benzimidazole**Step 1**Synthesis of 5-(2-fluorophenoxy)-6-hydroxy-2-pyrazine-2-yl-1H-benzimidazole

To tetrahydrofuran 10 ml and methanol 10 ml suspension of 5-benzyloxy-6-(2-fluorophenoxy)-2-pyrazine-2-yl-1H-benzimidazole 697 mg obtained in Example 250 was added 20 % palladium hydroxide-carbon catalyst 500 mg, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for one hour. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: ethyl acetate), and the title compound was obtained as yellow solid.

**Step 2**Production of 5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(2-cyano-pyrimidine-5-yloxy)-1H-benzimidazole

To N-methylpyrrolidinone 0.5 ml solution of 5-(2-fluorophenoxy)-6

-hydroxy-2-pyrazine-2-yl-1H-benzimidazole 7.0 mg obtained in Step 1 were added 5-bromo-2-cyano-pyrimidine 7.0 mg and cesium carbonate 15 mg, and thereafter the reaction liquor was stirred at 90°C for 15 minutes. The reaction mixture was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. By eliminating the solvent under reduced pressure, the title compound was obtained as a colourless solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 7.01-7.58 (5H, m), 7.64-7.82 (1H, m), 8.52 (2H, s), 8.67 (1H, s), 8.74 (1H, s), 9.44 (1H, s).

ESI-MS (m/e): 426 (M+H).

#### Example 252

##### 5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-cyano-pyridine-3-yloxy)-1H-benzimidazole

Using 5-(2-fluorophenoxy)-6-hydroxy-2-pyrazine-2-yl-1H-benzimidazole obtained in Example 251 (Step 1) and 5-bromo-2-cyanopyridine, the title compound was obtained as yellow solid by the same process as in Example 251 (Step 2), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 7.01-7.30 (5H, m), 7.42 (1H, dd, J = 8.6, 3.1 Hz), 7.55-7.77 (1H, m), 7.81 (1H, d, J = 8.6 Hz), 8.39 (1H, d, J = 3.1 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.47 (1H, s).

ESI-MS (m/e): 425 (M+H).

#### Example 253

##### 5-(2-fluoro-phenoxy)-2-pyrazine-2-yl-6-(6-trifluoromethyl-pyridine-3-yloxy)-1H-benzimidazole

To N-methylpyrrolidinone 1 ml solution of 21 mg of 5-(2-fluorophenoxy)-6-hydroxy-2-pyrazine-2-yl-1H-benzimidazole obtained in Example 251 (Step 1) were added 5-bromo-2-trifluoromethyl-pyridine 16 mg, cesium carbonate 50 mg and copper (II) oxide 10 mg, and thereafter the reaction liquor was stirred at 130°C for five hours. The precipitate was separated by filtration, and thereafter the solution was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, and thereafter was dried with anhydrous sodium sulphate. By eliminating the solvent under reduced pressure, the title compound was obtained as a brown solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 6.70-7.84 (6H, m), 7.49 (1H, dd, J = 8.8 Hz, 2.8 Hz), 7.78 (1H, d, J = 8.8 Hz), 8.39 (1H, d, J = 2.8 Hz), 8.73 (1H, s), 8.80 (1H, s), 9.49 (1H, s).

ESI-MS (m/e): 468 (M+H).

**Example 254**5-(2,6-difluoro-phenoxy)-4-fluoro-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole**Step 1**Synthesis of 2,3-difluoro-1-(6-methanesulphonyl-pyridine-3-yloxy)-4-nitro-benzene

To 3 ml N-methylpyrrolidinone solution of 2,3,4-trifluoro-nitrobenzene 135 mg were added 6-methanesulphonyl-pyridine-3-ol 112 mg and potassium carbonate 100 mg, and the reaction liquor was stirred at 50°C for one hour. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1), and the title compound was obtained.

**Step 2**Synthesis of N-(2,3-difluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-6-nitro-phenyl) pyrazine carboxamide

To methanol 3 ml solution of 2,3-difluoro-1-(6-methanesulphonyl-pyridine-3-yloxy)-4-nitro-benzene 22 mg were added 0.2 ml hydrazine monohydrate and about 0.01 g expanded Raney nickel catalysts, and the reaction liquor was stirred at room temperature for 15 minutes. The catalyst was eliminated by filtration by celite, and, by eliminating the solvent under reduced pressure, crude product was obtained. To pyridine 1 ml solution of the obtained crude product, pyrazine-2-carboxylic acid 12 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 25 mg were added, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To trifluoroacetic acid 2 ml solution of crude product, fuming nitric acid 0.1 ml was added, and the reaction liquor was stirred at 45°C overnight. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 20/1), and obtained the title compound.

**Step 3**Production of 5-(2,6-difluoro-phenoxy)-4-fluoro-2-pyrazine-2-yl-6-(6-methanesulphonyl-pyridine-3-yloxy)-1H-benzimidazole

To 0.5 ml N-methylpyrrolidinone solution of N-(2,3-difluoro-4-(6-methanesulphonyl-pyridine-3-yloxy)-6-nitro-phenyl) pyrazine carboxamide 8.6 mg were added 2,6-difluoro phenol 8 mg and potassium carbonate 8 mg, and the reaction liquor was stirred at

90°C for ten minutes, and thereafter, tin chloride (II) dihydrate 75 mg was added, and the reaction liquor was stirred at 90°C overnight. P-toluenesulfonic acid 3 mg was added furthermore, and the reaction liquor was stirred at 90°C for two hours. The precipitate was eliminated by filtration, and thereafter the solution was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a brown solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.22 (3H, s), 6.93-6.99 (2H, m), 7.01-7.10 (1H, m), 7.30-7.45 (1H, m), 7.47-7.51 (1H, m), 8.02 (1H, d, J = 8.6 Hz), 8.37 (1H, d, J = 2.3 Hz), 8.75 (1H, d, J = 2.3 Hz), 8.80 (1H, s), 9.56 (1H, s).

ESI-MS (m/e): 514 (M+H).

#### Example 255

##### 5-(2,6-difluoro-phenoxy)-7-fluoro-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

#### Step 1

##### Synthesis of 2,3-difluoro-1-(2,6-difluoro-phenoxy)-4-nitro-benzene

To 13 ml N-methylpyrrolidinone solution of 2,3,4-trifluoro-nitrobenzene 500 mg were added 2,6-difluoro-phenol 470 mg and tetrabutylammonium bromide 1.5 g, and the reaction liquor was stirred at 130°C overnight. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 4/1), and the title compound was obtained.

#### Step 2

##### Production of 5-(2,6-difluoro-phenoxy)-7-fluoro-2-pyridine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

2,3-difluoro-1-(2,6-difluoro-phenoxy)-4-nitro-benzene and 6-ethane sulfonyl-pyridin-3-ol obtained in Reference Example 4 were successively used, and, by the same process as in Example 254 (Step 2) and (Step 3), a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.91-6.96 (1H, m), 7.14 (2H, t, J = 8.4 Hz), 7.27-7.34 (1H, m), 7.48-7.54 (1H, m), 7.63 (1H, dd, J = 8.8, 2.7 Hz), 7.99 (1H, t, J = 7.6 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.31-8.37 (1H, m), 8.59 (1H, d, J = 2.7 Hz), 8.70-8.76 (1H, m).

ESI-MS (m/e): 527 (M+H).

#### Example 256

5-(pyridine-2-yloxy)-2-pyridine-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 2-hydroxypyridine, the title compound was obtained as a brown solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.09 (3H, s), 6.81 (1H, d, J = 8.2 Hz), 7.02 (2H, d, J = 8.6 Hz), 7.02-7.07 (1H, m), 7.49-7.54 (1H, m), 7.55 (1H, s), 7.63 (1H, s), 7.71-7.77 (1H, m), 7.83 (2H, d, J = 8.6 Hz), 7.98-8.03 (2H, m), 8.31 (1H, d, J = 7.6 Hz), 8.76 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 459 (M+H).

#### Example 257

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 2-difluoromethoxy-pyridin-3-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.10 (3H, s), 7.05 (2H, d, J = 8.4 Hz), 7.13-7.20 (1H, m), 7.33-7.70 (4H, m), 7.48 (1H, t, J = 72.8 Hz), 7.87 (2H, d, J = 8.4 Hz), 7.92 (1H, d, J = 4.5 Hz), 8.01 (1H, t, J = 7.4 Hz), 8.32 (1H, d, J = 7.8 Hz), 8.77 (1H, brs).

ESI-MS (m/e): 525 (M+H).

#### Example 258

5-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 1-methyl-2-oxo-1,2-dihydro-pyridin-3-ol, the title compound was obtained as a brown solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.04 (3H, s), 3.56 (3H, s), 6.06 (1H, td, J = 7.0, 2.7 Hz), 6.84 (1/2H, d, J = 7.4 Hz), 6.88 (1/2H, dd, J = 7.4, 1.8 Hz), 7.05-7.15 (3H, m), 7.20 (1/2H, s), 7.28 (1/2H, d, J = 1.2 Hz), 7.38 (1H, dd, J = 6.6, 4.7 Hz), 7.46 (1/2H, s), 7.60 (1/2H, s), 7.80-7.90 (3H, m), 8.36 (1H, t, J = 7.2 Hz), 8.62 (1H, d, J = 4.4 Hz).

ESI-MS (m/e): 489 (M+H).

#### Example 259



5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

## Step 1

Synthesis of 5-fluoro-4-(4-ethanesulfonyl-phenoxy)-2-nitro-phenylamine

Using 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

## Step 2

Production of 5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Using 5-fluoro-4-(4-ethanesulfonyl-phenoxy)-2-nitro-phenylamine and 2-difluoromethoxy-pyridin-3-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 14, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.20 (3H, t, J = 7.4 Hz), 3.15 (2H, q, J = 7.4 Hz), 7.04 (2H, d, J = 8.4 Hz), 7.06-7.15 (1H, m), 7.30-7.70 (4H, m), 7.46 (1H, t, J = 72.9 Hz), 7.80 (2H, d, J = 8.4 Hz), 7.89 (1H, d, J = 4.3 Hz), 7.99 (1H, t, J = 7.7 Hz), 8.30 (1H, d, J = 8.0 Hz), 8.74 (1H, brs)

ESI-MS (m/e): 539 (M+H).

## Example 260

5-(2-difluoromethoxy-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-difluoromethoxy-pyridine-3-yloxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 259 (Step 2), the title compound was obtained as a straw-coloured solid by the same process as in Example 197, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.27 and 1.28 (total 3H, each t, J = 7.4 Hz), 3.09 and 3.10 (total 2H, each q, J = 7.4 Hz), 6.98 and 6.99 (total 2H, each d, J = 9.0 Hz), 7.04-7.10 (1H, m), 7.23 and 7.42 (total 1H, each s), 7.25-7.30 (1H, m), 7.36 and 7.37 (total 1H, each t, J = 73.0 Hz), 7.52 and 7.73 (total 1H, each s), 7.80 and 7.81 (total 2H, each d, J = 9.0 Hz), 7.90-7.96 (1H, m), 8.58-8.63 (1H, m), 8.68 and 8.69 (total 1H, each d, J = 2.4 Hz), 9.61 and 9.63 (total 1H, each d, J = 1.5 Hz).

ESI-MS (m/e): 540 (M+H).

## Example 261

5-(2,4-difluoro-phenoxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-fluoro-5-(4-ethanesulfonyl-phenoxy)-2-nitro-phenylamine obtained in Example 259 (Step 1) and 2,4-difluoro-phenol, the title compound was obtained as a white solid by the same process as in Example 259, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.21 (3H, t, J = 7.4 Hz), 3.19 (2H, q, J = 7.4 Hz), 6.89-6.95 (1H, m), 7.01-7.12 (2H, m), 7.11 (2H, d, J = 8.4 Hz), 7.23-7.67 (3H, m), 7.84 (2H, d, J = 8.4 Hz), 7.99 (1H, t, J = 7.4 Hz), 8.29 (1H, d, J = 8.2 Hz), 8.75 (1H, brs)  
ESI-MS (m/e): 508 (M+H).

**Example 262**4-(1-methyl-1H-imidazol-2-yl sulphanyl)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

1-methyl-1H-imidazole-2-thiol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.09 (6H, s), 3.87 (3H, s), 6.69 (1H, s), 6.74 (1H, s), 6.79-6.89 (2H, m), 7.07 (2H, d, J = 8.4 Hz), 7.16 (1H, d, J = 2.0 Hz), 7.42 (2H, d, J = 8.4 Hz), 7.53 (1H, t, J = 7.6 Hz), 7.64 (1H, d, J = 2.0 Hz), 8.17 (1H, d, J = 7.4 Hz).

ESI-MS (m/e): 471 (M+H).

**Example 263**4-(pyridin-2-yl sulphanyl)-6-(4-dimethylcarbamoyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

Pyridine-2-thiol and 4-hydroxy-N,N-dimethylbenzamide were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 3.05 (3H, s), 3.09 (3H, s), 6.90-7.08 (4H, m), 7.30-7.65 (6H, m), 7.85 (1H, t, J = 7.5 Hz), 8.37 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 3.9 Hz), 8.62 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 468 (M+H).

**Example 264**4-(2,6-difluoro-phenoxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 4-methanesulphonyl-phenol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.22 (3H, s), 6.25 (1H, s), 7.16-7.24 (3H, m), 7.49-7.54 (1H, m), 7.60-7.66 (1H, m), 7.70-7.78 (1H, m), 7.95 (2H, d, J = 8.4 Hz), 8.02 (1H, m), 8.40 (1H, d, J = 4.7 Hz), 8.70 (1H, d, J = 2.3 Hz), 8.78 (1H, d, J = 2.3 Hz).

ESI-MS (m/e): 494 (M+H).

**Example 265**4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-methanesulphonyl-phenol were successively used, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.10 (3H, s), 3.63 (3H, s), 6.35 (1H, t, J = 7.1 Hz), 6.39 (1H, s), 7.06 (1H, s), 7.16 (2H, d, J = 8.0 Hz), 7.34 (1H, d, J = 7.2 Hz), 7.42-7.52 (1H, m), 7.53 (1H, dd, J = 6.8, 1.6 Hz), 7.90 (2H, d, J = 8.0 Hz), 7.91-8.00 (1H, m), 8.28-8.38 (1H, m), 8.71 (1H, s).

ESI-MS (m/e): 489 (M+H).

#### Example 266

##### 4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 6-methanesulphonyl-pyridin-3-ol obtained in Reference Example 3 were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.22 (3H, s), 6.39 (1H, s), 7.16-7.24 (2H, m), 7.21 (1H, d, J = 8.6 Hz), 7.32-7.40 (1H, m), 7.54-7.58 (1H, m), 8.06 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.3 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79 (1H, s), 9.56 (1H, s).

ESI-MS (m/e): 496 (M+H).

#### Example 267

##### 4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(6-methanesulphonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 266, the title compound was obtained by the same process as in Example 196 (Step 6), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.32 (3H, s), 6.47 (1H, s), 7.19-7.26 (3H, m), 7.34-7.42 (1H, m), 7.56-7.63 (2H, m), 8.05-8.11 (2H, m), 8.41 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.3 Hz), 8.83 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 495 (M+H).

#### Example 268

##### 4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 6-ethanesulfonyl-pyridin-3-ol obtained in Reference Example 4 were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.38 (1H, s), 7.10-7.25 (3H, m), 7.32-7.40 (1H, m), 7.56 (1H, dd, J = 8.6, 2.3 Hz), 8.06 (1H, d, J = 9.0 Hz), 8.48 (1H, d, J

= 2.7 Hz), 8.72 (1H, d, J = 2.7 Hz), 8.79 (1H, s), 9.56 (1H, s).

ESI-MS (m/e): 510 (M+H).

#### Example 269

4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 268, the title compound was obtained by the same process as in Example 196 (Step 6), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.44 (1H, s), 7.18-7.25 (3H, m), 7.32-7.41 (1H, m), 7.55-7.62 (2H, m), 8.03-8.09 (2H, m), 8.41 (1H, d, J = 7.8 Hz), 8.49 (1H, d, J = 2.3 Hz), 8.81 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 509 (M+H).

#### Example 270

4-(2-fluoro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyrazine-2-yl-1H-benzimidazole

2-fluoro-pyridin-3-ol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 68, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 3.23 (3H, s), 6.09 (1H, d, J = 2.3 Hz), 6.35 (1H, d, J = 2.3 Hz), 7.28 (1H, dd, J = 7.8, 5.5 Hz), 7.59-7.61 (1H, m), 7.66-7.67 (1H, m), 7.84-7.85 (1H, m), 8.6 (1H, d, J = 8.6 Hz), 8.70-8.74 (1H, m), 8.87 (1H, d, J = 2.3 Hz), 9.15 (1H, d, J = 1.6 Hz), 9.86 (1H, s).

ESI-MS (m/e): 479 (M+H).

#### Examples 271, 272

4-(2-fluoro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole and

4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

2-fluoro-pyridin-3-ol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Examples 108-1 and 108-2, a process based on these or a combination of these with a normal procedure, the title compound was respectively obtained.

4-(2-fluoro-pyridine-3-yloxy)-6-(6-methanesulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.23 (3H, s), 6.19 (1H, d, J = 2.3 Hz), 6.55 (1H, d, J = 2.3 Hz), 7.23 (1H, dd, J = 4.2, 2.1 Hz), 7.61-7.64 (2H, m), 7.67 (1H, dd, J = 8.6, 2.7 Hz), 7.84-7.85 (1H, m), 8.02

(1H, td, J = 7.8, 1.6 Hz), 8.09 (1H, d, J = 8-6 Hz), 8.16 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.68 (1H, d, J = 4-7 Hz).

ESI-MS (m/e): 478 (M+H).

6-(6-methanesulphonyl-pyridine-3-yloxy)-4-(2-oxo-1,2-dihydro-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 3.25 (3H, s), 6.61-6.62 (2H, m), 6.97-7.00 (2H, m), 7.63-7.67 (2H, m), 8.02-8.11 (4H, m), 8.56 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 4-7 Hz), 10.33 (1H, s)

ESI-MS (m/e): 476 (M+H).

**Example 273**

4-(2-fluoro-pyridine-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

2-fluoro-pyridin-3-ol and 4-methanesulphonyl-phenol were used successively, and, by the same process as in Example 67, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.13 (3H, s), 6.67 (1H, d, J = 2.0 Hz), 7.21-7.25 (2H, m), 7.35-7.39 (2H, m), 7.60-7.63 (1H, m), 7.77-7.82 (1H, m), 7.95-7.97 (2H, m), 8.00-8.09 (2H, m), 8.36 (1H, d, J = 8.2 Hz), 8.83 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 477 (M+H).

**Example 274**

4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

**Step 1**

Synthesis of 5-(4-ethanesulfonyl-phenoxy)-3-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-benzene-1,2-diamine

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-ethanesulphonyl-phenol were successively used, and, by the same process as in Example 67 (Step 1)-(Step 4), a process based on this or a combination of these with a normal procedure, the title compound was obtained as brown oily substance.

**Step 2**

Production of 4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

**Using**

5-(4-ethanesulfonyl-phenoxy)-3-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-benzene-1,2-diamine obtained in (Step 1), the title compound was obtained as a white solid by the same process

as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 3.65 (3H, s), 6.37 (1H, t, J = 7.2 Hz), 6.42 (1H, s), 7.09 (1H, s), 7.20 (2H, d, J = 8.8 Hz), 7.37 (1H, d, J = 6.6 Hz), 7.46-7.54 (1H, m), 7.55 (1H, d, J = 6.0 Hz), 7.88 (2H, d, J = 8.8 Hz), 7.94-8.02 (1H, m), 8.36 (1H, d, J = 7.6 Hz), 8.73 (1H, s).

ESI-MS (m/e): 503 (M+H).

#### Example 275

##### 4-(1-methyl-2-oxo-1,2-dihydro-pyridine-3-yloxy)-6-(4-(propane-2-sulfonyl)-phenoxy)-2-pyridine-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-(propane-2-sulfonyl)-phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.27 (6H, d, J = 6.8 Hz), 3.27-3.38 (1H, m), 3.65 (3H, s), 6.37 (1H, t, J = 7.4 Hz), 6.42 (1H, s), 7.10 (1H, s), 7.20 (2H, d, J = 8.8 Hz), 7.35-7.45 (1H, m), 7.47-7.54 (1H, m), 7.55 (1H, d, J = 6.8 Hz), 7.85 (2H, d, J = 8.8 Hz), 7.27-8.03 (1H, m), 8.30-8.40 (1H, m), 8.74 (1H, s).

ESI-MS (m/e): 517 (M+H).

#### Example 276

##### 4-(2,6-difluoro-phenoxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 268 and 1H-pyrazole-3-carboxaldehyde, the title compound was obtained by the same process as in Example 202, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 6.28-6.32 (1H, m), 7.09 (1H, s), 7.19 (2H, t, J = 8.2 Hz), 7.34 (1H, s), 7.52 (1H, t, J = 4.5 Hz), 7.83 (1H, s), 8.04 (1H, d, J = 8.6 Hz), 8.46 (1H, d, J = 2.7 Hz).

ESI-MS(m/e): 498 (M+H).

#### Example 277

##### 4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-(N,N-dimethylamino sulfonyl)-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-(N,N-dimethylamino sulfonyl)-phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a pale yellow

solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$  : 2.58 (6H, s), 3.48 (3H, s), 6.21 (1H, t, J = 7.1 Hz), 6.31 (1H, s), 6.91 (1H, s), 7.16 (2H, d, J = 8.8 Hz), 7.30 (1H, d, J = 6.4 Hz), 7.52 (1H, dd, J = 7.5, 5.7 Hz), 7.60 (1H, d, J = 5.1 Hz), 7.71 (2H, d, J = 8.8 Hz), 7.99 (1H, td, J = 7.8, 1.6 Hz), 8.27 (1H, d, J = 7.8 Hz), 8.73 (1H, d, J = 4.6 Hz).

ESI-MS(m/e): 518 (M+H).

#### Example 278

4-(2-chloro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

##### Step 1

Synthesis of 3-(2-chloro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine 2-chlorophenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and the title compound was obtained as brown oily substance by the process of Example 67 (Step 1) to (Step 4), by a method based on this, or by combining these with the normal method.

##### Step 2

Production of 4-(2-chloro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-chloro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in (Step 1), the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 6.9 Hz), 3.39 (2H, q, J = 6.9 Hz), 6.28 (1H, d, J = 2.0 Hz), 7.10-7.20 (1H, m), 7.28-7.31 (2H, m), 7.39-7.43 (1H, m), 7.57 (2H, td, J = 8.3, 4.2 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79-8.80 (1H, m), 9.58 (1H, s).

ESI-MS(m/e): 508 (M+H).

#### Example 279

4-(2-fluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole 2-fluoro-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.40 (1H, s), 7.10-7.20 (1H, m), 7.28-7.34 (4H, m), 7.57 (1H, dd, J = 8.6, 2.7 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79-8.80 (1H, m), 9.56 (1H, s).

ESI-MS(m/e): 492 (M+H).

#### Example 280

4-(2-trifluoromethyl-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazine

-2-yl-1H-benzimidazole

2-trifluoromethyl-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4Hz), 3.40 (2H, q, J = 7.4Hz), 6.50 (1H, d, J = 2.0Hz), 7.24 (2H, d, J = 7.8Hz), 7.38 (1H, t, J = 7.8Hz), 7.59 (1H, dd, J = 8.6, 2.7Hz), 7.64 (1H, t, J = 7.6Hz), 7.81 (1H, d, J = 7.8Hz), 8.06 (1H, d, J = 8.6Hz), 8.50 (1H, d, J = 2.7Hz), 8.71 (1H, d, J = 2.3Hz), 8.78-8.79 (1H, m), 9.54-9.55 (1H, m)

ESI-MS(m/e): 542 (M+H).

**Example 281**4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-cyclopropane sulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

3-hydroxy-1-methyl-1H-pyridin-2-one and 4-cyclopropane sulphonyl phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a pale yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.01-1.15 (4H, m), 2.81-2.90 (1H, m), 3.51 (3H, s), 6.24 (1H, t, J = 7.0 Hz), 6.35 (1H, d, J = 2.0 Hz), 6.95 (1H, d, J = 2.0 Hz), 7.18 (2H, d, J = 9.0 Hz), 7.33 (1H, dd, J = 7.5, 1.8 Hz), 7.53-7.57 (1H, m), 7.63 (1H, dd, J = 6.8, 1.8 Hz), 7.87 (2H, d, J = 9.0 Hz), 8.02 (1H, td, J = 7.8, 1.8 Hz), 8.31 (1H, d, J = 8.0 Hz), 8.75 (1H, d, J = 4.1 Hz).

ESI-MS(m/e): 515 (M+H).

**Example 282**4-(2,6-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-(1-methyl-pyrazol-3-yl)-1H-benzimidazole

Using 1H-1-methyl-pyrazole-3-carboxylic acid and 3-(2,6-difluoro-phenoxy)-5-(6-ethane sulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 268, the title compound was obtained by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 4.12 (3H, s), 6.61 (1H, s), 7.19 (1H, d, J = 2.3 Hz), 7.22 (1H, s), 7.25 (2H, dd, J = 5.6, 2.3 Hz), 7.37-7.43 (1H, m), 7.62 (1H, dd, J = 8.6, 2.7 Hz), 7.93 (1H, d, J = 2.3 Hz), 8.08-8.09 (1H, m), 8.51 (1H, d, J = 2.3 Hz).

ESI-MS(m/e): 512 (M+H).

**Example 283**4-(3-trifluoromethyl-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

3-trifluoromethyl-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the



same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.39 (1H, s), 7.25-7.37 (5H, m), 7.57 (1H, dd, J = 4.3, 2.2 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.7 Hz), 8.79 (1H, s), 9.56 (1H, s)

ESI-MS(m/e): 542 (M+H).

#### Example 284

##### 4-(4-trifluoromethyl-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

4-trifluoromethyl-phenol and 6-ethane sulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.80 (1H, s), 7.32 (2H, d, J = 8.6 Hz), 7.66-7.64 (1H, m), 7.72 (2H, d, J = 8.6 Hz), 8.08 (1H, d, J = 9.0 Hz), 8.54-8.56 (1H, m), 8.70-8.73 (1H, m), 8.78 (1H, s), 9.50 (1H, s)

ESI-MS(m/e): 542 (M+H).

#### Example 285

##### 4-(2,3-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

2,3-difluoro-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and the title compound was obtained by the same process as in Example 278, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.3 Hz), 3.40 (2H, q, J = 7.3 Hz), 6.59 (1H, d, J = 1.6 Hz), 7.12-7.18 (4H, m), 7.60 (1H, dd, J = 9.0, 2.7 Hz), 8.07 (1H, dd, J = 8.6, 0.8 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.79 (1H, dd, J = 2.7, 1.4 Hz), 9.53 (1H, d, J = 1.6 Hz).

ESI-MS(m/e): 510 (M+H).

#### Example 286

##### 4-(2-cyano-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2-cyanophenol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.23 (3H, s), 6.86 (1H, d, J = 2.0 Hz), 7.21 (1H, d, J = 8.2 Hz), 7.33-7.37 (2H, m), 7.62-7.67 (3H, m), 7.84 (1H, d, J = 7.8 Hz), 8.04-8.11 (2H, m), 8.36 (1H, d, J = 7.8 Hz), 8.54 (1H, d, J = 2.7 Hz), 8.82 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 484 (M+H).

**Example 287**

4-(2,4-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2 -yl-1H-benzimidazole

2,4-difluoro-phenol and 6-ethane sulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.11 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.51 (1H, d, J = 2.0 Hz), 7.05-7.10 (2H, m), 7.37-7.39 (1H, m), 7.46-7.59 (3H, m), 7.98-8.02 (2H, m), 8.26 (1H, d, J = 7.8 Hz), 8.56 (1H, d, J = 2.7 Hz), 8.73 (1H, d, J = 4.3 Hz)

ESI-MS(m/e): 509 (M+H).

**Example 288**

4-(pyridin-2-yl sulphanyl)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Pyridine-2-thiol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.22 (3H, s), 7.03 (1H, d, J = 8.0 Hz), 7.06-7.10 (1H, m), 7.34 (1H, d, J = 2.1 Hz), 7.37-7.41 (1H, m), 7.43 (1H, dd, J = 8.8, 2.8 Hz), 7.52 (1H, td, J = 7.8, 2.2 Hz), 7.64 (1H, d, J = 2.1 Hz), 7.88 (1H, td, J = 7.8, 1.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.39 (1H, d, J = 7.8 Hz), 8.45 (1H, dd, J = 4.9, 1.0 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.64 (1H, d, J = 4.1 Hz).

ESI-MS(m/e): 476 (M+H).

**Example 289**

4-(2,6-difluoro-phenoxy)-6-(6-ethane sulfonyl-pyridin-3-yloxy)-5-fluoro-2 -pyrazin-2-yl -1H-benzimidazole

2,6-difluoro-phenol, 6-ethane sulfonyl-pyridin-3-ol and pyrazine-2-carboxylic acid were successively used, and, by the same process as in Example 119, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30 and 1.32 (total 3H, each t, J = 7.4 Hz), 3.38 and 3.40 (total 2H, each q, J = 7.4 Hz), 6.96-7.03 (2H, m), 7.10-7.20 (1H, m), 7.14 and 7.52 (total 1H, each d, J = 6.0 Hz), 7.34 and 7.38 (total 1H, each dd, J = 8.6, 2.8 Hz), 8.03 and 8.06 (total 1H, each d, J = 8.6 Hz), 8.48 and 8.52 (total 1H, each d, J = 2.8 Hz), 8.55-8.72 (2H, m), 9.38 and 9.62 (total 1H, each d, J = 1.5 Hz).

ESI-MS(m/e): 528 (M+H).

**Example 290**4-(2,6-difluoro-phenoxy)-6-(6-ethane  
sulfonyl-pyridin-3-yloxy)-5-fluoro-2-pyridin-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-4-fluoro-5-(6-ethane sulfonyl-pyridin-3-yloxy) -benzene -1,2-diamine obtained in Example 289, the title compound was obtained as a brown solid by method of Example 196 (Step 6), a method based on this, or a combination of these with a normal method.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.94-7.01 (2H, m), 7.04-7.50 (4H, m), 7.79-7.95 (1H, m), 7.99-8.07 (1H, m), 8.23 and 8.37 (total 1H, each d, J = 7.0 Hz), 8.48 (1H, s), 8.60-8.68 (1H, m)

ESI-MS(m/e): 527 (M+H).

**Example 291**4-(2,6-difluoro-phenoxy)-6-(6-ethane  
sulfonyl-pyridine-3-yloxy)-5-fluoro-2-(1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-4-fluoro-5-(6-ethanesulfonyl-pyridin-3-yloxy) benzene-1,2-diamine obtained in Example 289, and 1H-1-methyl-pyrazole-3-carboxylic acid, the title compound was obtained as a pale yellow solid by the same process as in Example 203, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.23 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 4.02 (3H, s), 6.94 (1H, s), 7.01-7.12 (2H, m), 7.14-7.23 (1H, m), 7.29 (1H, d, J = 5.4 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.70 (1H, s), 8.06 (1H, d, J = 8.6 Hz), 8.50 (1H, s)

ESI-MS(m/e): 530 (M+H).

**Example 292**4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-5-fluoro-2-pyridin-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 290, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 3.21 (3H, s), 6.98 (2H, t, J = 8.0 Hz), 7.05-7.50 (4H, m), 7.80-7.93 (1H, m), 8.03 (1H, t, J = 8.8 Hz), 8.23 and 8.37 (total 1H, each d, J = 8.4 Hz), 8.47 (1H, s), 8.61 and 8.67 (total 1H, each s).

ESI-MS(m/e): 513 (M+H).

**Example 293**1-(2-(6-(4-[2-hydroxy-ethyl]-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-bromo phenethyl-alcohol, the title compound was obtained as a white solid the same method as in an example 122, a method based on this, or a combination of these with a normal method.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.05-2.90 (10H, m), 3.00-4.45 (4H, m), 5.20-5.45 (1H, m), 6.80-7.70 (7H, m), 7.85-7.95 (1H, m), 8.20-8.45 (1H, m), 8.50-8.80 (1H, m)

ESI-MS(m/e): 443 (M+H).

#### Example 294

1-(2-(6-(4-[5-methyl-[1,3,4]oxadiazol-2-yl]-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 2-(4-bromophenyl)-5-methyl-[1,3,4] oxadiazole, the title compound was obtained as a colourless oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-2.80 (10H, m), 3.50-3.95 (2H, m), 5.10-5.50 (1H, m), 6.90-7.60 (5H, m), 7.82-8.10 (3H, m), 8.35-8.45 (1H, m), 8.60-8.75 (1H, m).

ESI-MS(m/e): 481 (M+H).

#### Example 295

1-(2-(6-(4-[2-methyl-oxazol-5-yl]-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-(4-bromophenyl)-2-methyl-oxazole, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.66-2.66 (10H, m), 3.53-3.94 (2H, m), 5.21-5.57 (1H, m), 6.93-7.92 (9H, m), 8.30-8.69 (2H, m), 10.61-10.97 (1H, m)

ESI-MS(m/e): 480 (M+H).

#### Example 296

2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.84-2.16 (3H, m), 2.24-2.43 (1H, m), 3.12 and 3.14 (total 3H, each s), 3.49-4.24 (4H, m), 5.17-5.38 (1H, m), 7.20-7.58 (5H, m), 7.93-8.04 (3H, m), 8.26-8.30 (1H, m), 8.73 (1H, s)

ESI-MS(m/e): 493 (M+H).

## Examples 297, 298

1-(2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone.1-(2-(6-(5-chloro-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-chloro-2-ethane sulfonyl-pyridine, the title compounds were respectively obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

1-(2-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.00-1.34 (3H, m), 1.44-2.41 (7H, m), 3.11-3.89 (4H, m), 5.05-5.47 (1H, m), 6.73-8.72 (9H, m), 10.89-11.47 (1H, m).

ESI-MS(m/e): 492 (M+H).

1-(2-(6-(5-chloro-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.51-2.33 (7H, m), 3.41-3.90 (2H, m), 5.03-5.45 (1H, m), 6.79-8.67 (9H, m), 10.80-11.00 (1H, m).

ESI-MS(m/e): 434 (M+H).

## Example 299

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A and enantiomer BStep 1Synthesis of 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To 1 ml of a pyridine solution of 53 mg 1-(2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidin-1-yl)-2,2,2-trifluoro-ethanone obtained from Example 162 (Step 6) were added successively pyrazine-2-carboxylic acid 14.5 mg, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 27.0 mg, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was diluted with saturated aqueous sodium chloride solution and extraction was carried out with ethyl acetate. The organic layers were combined, and washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium bicarbonate and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was dissolved in toluene 1 ml, and p-toluenesulfonic acid monohydrate 9.9 mg

was added, and the reaction liquor was stirred at 120°C for six hours. After cooling, the reaction liquor was diluted with ethyl acetate, washed successively with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was refined by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1), and the title compound was obtained as oily substance.

### Step 2

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole

To a solution of 2,2,2-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 40 mg dissolved in a mixture of methanol 1.6 ml and water 0.4 ml was added potassium carbonate 55 mg, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was concentrated under reduced pressure, and saturated ammonium chloride aqueous solution was added to the residue and thereafter, it was extracted with chloroform and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and it was refined by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol/aqueous ammonia = 90/10/1) and the title compound was obtained as oily substance.

### Step 3

Production of 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A and enantiomer B

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole 7.2 mg was optically-resolved on optical resolution column (CHIRALPAK AD 2cm phi x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: hexane/ethanol/diethylamine 20/80/0.1, flow rate 10 ml/min) and enantiomer A (retention time: 21.5 min), enantiomer B (retention time = 25.3 min) were respectively obtained as a yellow oily substance.

### Example 300

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone Enantiomer A

Using 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A obtained in Example 299, the title compound was obtained as an oily substance by the same process as in Example 164, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.42 (7H, m), 3.00-3.09 (3H, m), 3.57-3.90 (2H, m), 5.10-5.43 (1H, m), 7.02-8.00 (6H, m), 8.57-8.73 (2H, m), 9.55-9.48 (1H, m).

ESI/MS(m/e): 478 (M+H).

#### Example 301

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B

Using 5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 299, the title compound was obtained as an oily substance by the same process as in Example 164, a process based on this or a combination of these with a normal procedure.

ESI-MS(m/e): 478 (M+H).

#### Example 302

1-(2-(6-(6-[propane-2-sulfonyl]-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-chloro-2-(propane-2-sulfonyl)-pyridine, the title compound was obtained by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.11-1.40 (6H, m), 1.55-2.43 (7H, m), 3.54-3.89 (3H, m), 5.11-5.48 (1H, m), 6.67-8.72 (9H, m), 11.00-11.69 (1H, m)

ESI-MS (m/e): 506 (M+H).

#### Example 303

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-phenyl-propan-1-one

Using 3-phenyl-propionic acid, the title compound was obtained as a colourless oily material by the same method as in an example 296, a method based on this, or a method which combined these and the normal method.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.10-3.10 (11H, m), 3.40-4.00 (2H, m), 4.90-5.30 (1H, m), 6.80-8.00 (13H, m), 8.30-8.50 (1H, m), 8.60-8.75 (1H, m), 10.50-11.20 (1H, m).

ESI-MS(m/e): 567 (M+H).

#### Example 304

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethane thione

To 1 ml of chloroform solution of 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B 20mg obtained in Example 163,

ethyl dithioacetate 0.010 ml were added, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was diluted with chloroform, then washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and it was refined by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1), to obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50-2.80 (7H, m), 3.00-3.20 (3H, m), 3.60-4.40 (2H, m), 5.30-5.50 (1H, m), 7.00-7.60 (5H, m), 7.80-8.00 (3H, m), 8.30-8.50 (1H, m), 8.60-8.75 (1H, m).

ESI-MS(m/e): 493 (M+H).

#### Example 305

##### 2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using sodium fluoroacetate, the title compound was obtained by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.67-2.40 (4H, m), 3.00-3.13 (3H, m), 3.51-4.00 (2H, m), 4.48-5.06 (2H, m), 5.18-5.46 (1H, m), 7.02-7.69 (5H, m), 7.80-7.98 (3H, m), 8.34-8.44 (1H, m), 8.53-8.70 (1H, m), 10.82-11.12 (1H, m).

ESI-MS(m/e): 495 (M+H).

#### Example 306

##### 1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

##### Step 1

##### Synthesis of 4-bromo-5-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine

To N,N-dimethylformamide 50 ml solution of 4-bromo-5-fluoro-2-nitrophenyl amine 6.4 g, 4-methanesulphonyl-phenol 5.2 g, potassium carbonate 5.7 g were added successively, and the reaction liquor was stirred at 120°C for three hours. Water 200 ml was added to the reaction liquor and the precipitated solid was recovered by filtration and was dried, and the title compound was obtained as a brown solid.

##### Step 2

##### Synthesis of 2-(4-amino-2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1- carboxylic acid t-butyl ester

To a solution of 4-bromo-5-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine 10.3 g in dimethoxyethane 100 ml, 1-(t-butoxycarbonyl) pyrrole-2-boronic acid 7.9 g, dichlorobis triphenyl phosphine palladium 1.8 g, saturated sodium carbonate aqueous solution 50 ml and water 50 ml



were added successively, and under a nitrogen atmosphere, the reaction liquor was stirred at 80°C for one hour. After cooling, the reaction liquor was filtered with cellite, and the filtrate was diluted with ethyl acetate, and washed successively with water, saturated aqueous sodium chloride solution and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained as brown oily substance.

### Step 3

Synthesis of 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester

To a solution of 2-(4-amino-2-(4-methanesulphonyl-phenoxy)-5-nitro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 12g in 2-propanol 200 ml, water 20 ml, 5 % platinum-carbon catalyst 4 g were added, and the reaction liquor was stirred at 70°C under hydrogen pressure atmosphere of 50 kgf/cm<sup>2</sup> for two days. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as dark brown oily substance.

### Step 4

Synthesis of 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole

To solution of 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 500 mg in pyridine 10 ml were successively added 5-bromopyridine-2-carboxylic acid 220 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 260 mg, and the reaction-liquor was stirred at room temperature for 12 hours. The reaction liquor was diluted with chloroform, and it was washed successively with water, saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was dissolved in trifluoroacetic acid 10 ml, and the reaction liquor was heated under reflux for three hours. After cooling, the reaction liquor was distilled off under reduced pressure, and the obtained residue was diluted with chloroform, and it was made basic with saturated aqueous sodium bicarbonate, then, the organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent : chloroform/methanol/aqueous ammonia = 50/1/0.1) and the title compound was obtained as a colourless oily substance.

## Step 5

Production of 1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

To solution of 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole 220 mg in pyridine 2 ml, was added acetic anhydride 0.050 ml, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (chloroform/methanol/aqueous ammonia = 50/1/0.1), and the title compound was obtained as pale-brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.40 (7H, m), 2.90-3.15 (3H, m), 3.50-3.90 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.05 (3H, m), 8.20-8.35 (1H, m), 8.60-8.80 (1H, m), 10.50-11.05 (1H, m)

ESI-MS(m/e): 555, 557 (M+H).

## Example 307

1-(2-(2-(6-fluoro-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester and 6-fluoro-pyridine-2-carboxylic acid, the title compound was obtained the same process as in Example 306 (Step 4) (Step 5), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.70-2.40 (7H, m), 2.98-3.11 (3H, m), 3.57-3.90 (2H, m), 5.07-5.51 (1H, m), 6.81-8.32 (9H, m), 10.64-11.36 (1H, m).

ESI-MS(m/e): 495 (M+H).

## Example 308

1-(2-(2-pyridin-2-yl-6-(6-trifluoromethyl-pyridin-3-yloxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-bromo-2-trifluoromethyl-pyridine, the title compound was obtained as a pale yellow solid by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.89 and 2.14 (total 3H, each s), 1.90-2.20 (3H, m), 2.24-2.50 (1H, m), 3.63-3.99 (2H, m), 5.26-5.40 (1H, m), 7.34-7.63 (4H, m), 7.80-7.86 (1H, m), 7.94-8.02 (1H, m), 8.29-8.37 (1H, m), 8.58-8.59 (1H, m), 8.73-8.78 (1H, m).

ESI-MS(m/e): 468 (M+H).

**Example 309****1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone Enantiomer A****Step 1****Synthesis of 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B**

1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone 2.2 g obtained from Example 121 (Step 8) were optically-resolved on column for optical resolution (CHIRALPAK AS 2cm phi x 25 cmL (Daicel Chemical Industries Ltd), mobile phase: hexane/ethanol 30/70, flow rate: 15 ml/min), and enantiomer A (retention time = 11.43min), enantiomer B (retention time = 16.32min) were respectively obtained as black solids.

**Step 2****Production of 1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A**

Using the 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer A obtained from Example 309 (Step 1) and 5-chloro-2-methanesulphonyl-pyridine, the title compound was obtained as an oily substance by the process of Example 121 (Step 9) - (Step 12), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.42 (7H, m), 3.16-3.27 (3H, m), 3.57-3.91 (2H, m), 5.14-5.34 (1H, m), 7.04-8.10 (6H, m), 8.31-8.70 (3H, m), 10.59-10.94 (1H, m).

ESI-MS(m/e): 478 (M+H).

**Example 310****1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B**

Using the 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer B obtained from Example 309 (Step 1), the title compound was obtained as an oily substance by the same process as in Example 309, a process based on this or a combination of these with a normal procedure.

ESI-MS(m/e): 478 (M+H).

**Example 311****(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-pyridin-2-yl-methanone**

Using pyridine-2-carboxylic acid and 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained by the same process as in Example 296, a process based on this or a

combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.60-2.45 (4H, m), 2.91-3.09 (3H, m), 3.71-4.30 (2H, m), 5.44-5.60 and 5.91-6.03 (total 1H, each m), 6.77-7.93 (11H, m), 8.10-8.66 (3H, m), 10.82-11.00 (1H, m).

ESI-MS(m/e): 540 (M+H).

#### Example 312

(2-fluoro-phenyl)-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-methanone

Using 2-fluorobenzoic acid and 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.51 (4H, m), 2.90-3.08 (3H, m), 3.40-4.08 (2H, m), 4.91-5.02 and 5.46-5.60 (total 1H, each m), 6.55-8.69 (15H, m)

ESI-MS(m/e): 557 (M+H).

#### Example 313

6-(1-acetyl pyrrolidin-2-yl)-5-(4-fluoro phenoxy)-2-isoxazol-3-yl-1H-benzimidazole

Using isoxazole-3-carbaldehyde, the title compound was obtained by the same process as in Example a process based on this or a combination of these with a normal procedure process same as Example 189, this, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.46 (4H, m), 1.87 and 2.16 (total 3H, eachs), 3.58-3.88 (2H, m), 5.13-5.1.7 and 5.52-5.55 (total 1H, each m), 6.85-7.40 (7H, m), 8.56 (1H, s).

ESI-MS(m/e): 407 (M+H).

#### Example 314

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2- carbonitrile

Using the 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer B obtained from Example 309 (Step 1) and 2-cyano-5-bromo-pyridine, the title compound was obtained as a white solid by the same process as in Example 309, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.53-2.42 (7H, m), 3.40-3.50 (2H, m), 5.07-5.29 (1H, m), 7.00-7.94 (6H, m), 8.28-8.68 (3H, m), 11.00-11.52 (1H, m).

ESI-MS(m/e): 425 (M+H).

#### Example 315

(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-methyl-carbamic acid t-butyl ester

Using N-t-butoxycarbonyl-glycine and 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-

pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 163, the title compound was obtained by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.20-1.69 (16H, m), 2.76-3.12 (7H, m), 5.15-5.26 (1H, m), 7.00-7.44 (5H, m), 7.76-8.00 (4H, m), 8.28-8.40 (1H, m), 8.58-8.73 (1H, m).

ESI-MS(m/e): 606 (M+H).

#### Example 316

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-methylamino-ethanone

Using (2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-methyl-carbamic acid t-butyl ester obtained in Example 315, the title compound was obtained by the same process as in Example 171, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-1.97 (4H, m), 2.20-2.46 (3H, m), 2.94-3.08 (5H, m), 3.19-3.90 (2H, m), 5.15-5.43 (1H, m), 7.08-7.65 (5H, m), 7.87-7.94 (3H, m), 8.36-8.38 (1H, m), 8.64 (1H, s).

ESI-MS(m/e): 506 (M+H).

#### Example 317

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

##### Step 1

Synthesis of 2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid t-butyl ester

To solution of the 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained from Example 306 (Step 3), 49.0 mg, in N,N-dimethylformamide 1 ml was added 1H-pyrazole-3-carboxaldehyde 10.0 mg, and the reaction liquor was stirred at 90°C one overnight. After cooling, the reaction liquor was diluted with ethyl acetate and was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1) and the title compound was obtained as a brown solid.

##### Step 2

Production of 1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-n-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidine-1-c

arboxylic acid t-butyl ester 49.2 mg was dissolved in 4N hydrochloric acid-dioxane 1 ml, and the reaction liquor was stirred at room temperature for two hours. Reaction solvent was eliminated by distillation under reduced pressure, and acetic anhydride 0.012 ml was added to a solution of the obtained residue in pyridine 2 ml, and the mixture was stirred at room temperature for 30 minutes. Reaction solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1) and the title compound was obtained as a brown solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.53-2.38 (7H, m), 2.97-3.10 (3H, s), 3.39-3.99 (2H, m), 5.06-5.31 (1H, m), 6.80-8.04 (8H, m).  
ESI-MS(m/e): 466 (M+H).

**Example 318**

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using the 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl) -pyrrolidine-1- carboxylic acid t-butyl ester obtained from Example 306 (Step 3) and 1-methyl-1H-pyrazole-3-carboxylic acid, the title compound was obtained as a white solid by the same process as Example 306 (Step 4), (Step 5), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.70-2.37 (7H, m), 2.98-3.11 (3H, m), 3.52-4.02 (5H, m), 5.04-5.43 (1H, m), 6.74-7.67 (6H, m), 7.79-7.97 (2H, m), 10.38-11.00 (1H, m).

ESI-MS(m/e): 480 (M+H).

**Example 319**

1-(2-(2-(5-fluoro-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone.

Using 5-fluoro-pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 318, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.50 (7H, m), 2.85-3.20 (3H, m), 3.50-4.00 (2H, m), 5.00-5.50 (1H, m), 6.80-8.10 (7H, m), 8.20-8.60 (2H, m), 10.50-11.20 (1H, m).

ESI-MS(m/e): 495 (M+H).

**Example 320**

(1-amino-cyclopropyl)-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-methanone

Using 1-amino-cyclopropanecarboxylic acid, the title compound was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 0.80-1.10 (4H, m), 1.88-2.17 (3H, m), 2.32-2.40 (1H, m), 3.12 (3H, s), 4.06 (2H, brs), 5.21 (1H, brs), 7.18-7.54 (5H, m), 7.91-7.99 (3H, m), 8.27 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 4.3 Hz).

ESI-MS(m/e): 518 (M+H).

#### Example 321

5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile

Using 1-(2-(4,5-diamino-2-benzyloxy-phenyl)-pyrrolidin-1-yl)-ethanone enantiomer B obtained in Example 309 (Step 1) and pyrazine-2-carboxaldehyde, the title compound was obtained as an oily substance by the same process as in Example 314, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.67-2.47 (7H, m), 3.60-3.92 (2H, m), 5.11-5.35 (1H, m), 7.00-7.77 (4H, m), 8.47-8.73 (3H, m), 9.52-9.68 (1H, m), 10.88-11.94 (1H, m).

ESI-MS(m/e): 426 (M+H).

#### Example 322

1-(2-(2-(5-cyano-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-cyano-pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.05-2.40 (7H, m), 2.80-3.20 (3H, m), 3.60-4.00 (2H, m), 5.05-5.45 (1H, m), 6.90-7.80 (4H, m), 7.80-8.00 (2H, m), 8.05-8.20 (1H, m), 8.40-8.60 (1H, m), 8.80-9.00 (1H, m), 10.40-10.80 (1H, m).

ESI-MS(m/e): 502 (M+H).

#### Example 323

1-(2-(2-(4-chloro-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-chloro-pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.67-2.40 (7H, m), 3.00-3.13 (3H, m), 3.54-3.91 (2H, m), 5.10-5.44 (1H, m), 6.79-7.52 (5H, m), 7.64-7.97 (2H, m), 8.36-8.57 (2H, m), 10.75-11.24 (1H, m).

ESI-MS(m/e): 511 (M+H).

#### Example 324

1-(2-(2-(5-ethoxy-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

din-1-yl)-ethanone

Using 5-ethoxy-pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.00-3.40 (10H, m), 3.60-4.00 (3H, m), 4.20-5.20 (4H, m), 5.80-6.40 (1H, m), 7.20-9.20 (9H, m), 11.50-12.00 (1H, m).

ESI-MS(m/e): 521 (M+H).

**Example 325**Trans-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanoneStep 1Synthesis of 1-(2-fluoro-4-nitro-phenyl)-3-butene-1-ol

To a solution of 4-nitro-2-fluoro-benzaldehyde (synthesised according to process described in US6239152) 2.00 g in chloroform 12 ml, was added titanium tetrachloride 0.65 ml, and the reaction liquor was stirred at room temperature for ten minutes, and thereafter, allyl-trimethyl-silane 2.4 ml was added, and the reaction liquor was stirred at room temperature for 20 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained as reddish yellow solid.

**Step 2**Synthesis of N-(1-(2-fluoro-4-nitro-phenyl)-3-butenyl)-acetamide

To solution of 1-(2-fluoro-4-nitro-phenyl)-3-butene-1-ol 480 mg in chloroform 10 ml were added, methanesulfonyl chloride 0.29 ml and triethylamine 0.63 ml, and thereafter the reaction liquor was stirred at room temperature for 15 minutes. The reaction liquor was washed using water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and crude product was obtained as pale yellow oily substance. To solution of crude product in dimethylformamide 10 ml was added sodium azide 310 mg, and the reaction liquor was stirred at 45°C for 30 minutes. The reaction liquor was diluted with ethyl acetate and was washed using water, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and crude product was obtained as brown oily substance. To solution of the obtained crude product in tetrahydrofuran 10 ml were added triphenyl phosphine 1.0 g and water 2 ml, and the reaction liquor was stirred while heating under reflux for 12 hours. 1 N hydrochloric acid was added to the reaction liquor, and the organic layer was eliminated, and thereafter the aqueous layer was made basic using 1N sodium hydroxide



aqueous solution. Extraction with chloroform was carried out, and it was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and crude product 380 mg was obtained as brown oily substance. To solution of crude product 380 mg in chloroform 10 ml were added triethylamine 0.50 ml, acetic anhydride 0.25 ml and 4-dimethylaminopyridine 20 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol 50/1) and the title compound was obtained as brown oily substance.

### Step 3

#### Synthesis of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4-hydroxy-pyrrolidine

To solution of N-(1-(2-fluoro-4-nitro-phenyl)-3-butenyl)-acetamide 200 mg in tetrahydrofuran 4 ml were added water 1 ml and iodine 600 mg, then the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with chloroform, and it was washed successively with saturated aqueous sodium bicarbonate, saturated sodium thiosulfate aqueous solution, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To solution of crude product in chloroform 5 ml were added triethylamine 0.25 ml, acetic anhydride 0.13 ml and 4-dimethylaminopyridine 10 mg, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and potassium carbonate 20 mg was added to methanol 5 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and thereafter the residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 30/1) and the title compound was obtained as diastereomer mixture of colourless solid.

### Step 4

#### Synthesis of 1-acetyl-2-(2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine

Acetic anhydride 0.06 ml was added to pyridine 2 ml solution of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4-hydroxy-pyrrolidine 140 mg, and the reaction liquor was stirred overnight at 50°C. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate) and product 150 mg was obtained. Expanded Raney nickel catalyst about 50 mg was added to methanol 3 ml solution of product 57 mg, and the reaction liquor was stirred under a hydrogen atmosphere for 30 minutes, and thereafter, catalyst was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure. Pyridine-2-carboxylic acid 30 mg and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 50 mg were added to

pyridine 2 ml solution of the residue, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

#### Step 5

Synthesis of trans-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine and cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine  
Fuming nitric acid 0.1ml was added to trifluoroacetic acid 0.5 ml solution of 1-acetyl-2-(2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine 36 mg, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and thereafter the residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 15/1) and diastereomer mixture 30 mg of the title compound was obtained as a white solid. It was refined further by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 15/1) and single diastereomers of the title compound were respectively obtained as yellow solid. (Rf value = trans isomer > cis isomer).

#### Step 6

Production of trans-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

4-methanesulphonylphenol 10 mg and cesium carbonate 20 mg were added to dimethylformamide 0.5 ml solution of trans-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine 21 mg, and the reaction liquor was stirred at 90°C for one hour. Tin (II) chloride dihydrate 100 mg was added, and the reaction liquor was stirred at 90°C for five hours. The reaction liquor was diluted with ethyl acetate, and it was washed successively using water, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.50-1.90 (3H, m), 2.10-2.53 (2H, m), 2.98 (3H, s), 3.60-3.90 (2H, m), 5.13-5.26 (2H, m), 7.03-7.65 (5H, m), 7.78-7.87 (3H, m), 8.10-8.18 (1H, m), 8.59 (1H, s).

ESI-MS(m/e): 535 (M+H).

#### Example 326

Trans-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-ethanone

25 % sodium methoxide 0.015 ml was added to solution of trans-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 325) 40 mg in methanol 2 ml, and the reaction liquor was stirred at room temperature for ten minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (YMC Corporation) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The title compound was obtained as a white solid by eliminating the solvent by distillation under reduced pressure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.48-2.80 (5H, m), 2.99-3.10 (3H, m), 3.48-4.10 (2H, m), 4.40-4.60 (1H, m), 5.25-5.50 (1H, m), 7.00-7.50 (5H, m), 7.75-8.00 (3H, m), 8.24-8.48 (1H, m), 8.48-8.70 (1H, m), 10.70-11.20 (1H, m).

ESI-MS(m/e): 493 (M+H).

#### Example 327

##### Cis-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Bis (2-methoxyethyl) amino sulphur tri fluoride 0.02 ml was added to a solution of trans-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 326) 10 mg in chloroform 1 ml, and the reaction liquor was stirred at room temperature for ten minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 15/1) and the title compound was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.92 (3H x 1/2, s), 2.22 (3H x 1/2, s), 2.22-2.80 (2H, m), 3.13 (3H x 1/2, s), 3.15 (3H x 1/2, s), 3.80-4.40 (2H, m), 5.20-5.50 (2H, m), 7.20-7.80 (5H, m), 7.90-8.10 (3H, m), 8.28 (1H, t, J = 7.8 Hz), 8.74 (1H, brs).

ESI-MS(m/e): 495 (M+H).

#### Example 328

##### Cis-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using the cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained from Example 325 (Step 5), the title compound was obtained as a colourless solid by the same process as Example 325 (Step 6), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.40-1.90 (3H, m), 2.20-2.55 (2H, m), 3.00 (3H, s), 3.62-3.90 (2H, m),

5.12-5.28 (2H, m), 6.98-7.75 (5H, m), 7.78-7.88 (3H, m), 8.11-8.19 (1H, m), 8.60 (1H, s).

ESI-MS(m/e): 535 (M+H).

#### Example 329

Cis-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using cis-1-(4-acetoxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 328, the title compound was obtained as a colourless solid by the same process as in Example 326, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.80-2.00 (3H, m), 2.04-2.75 (2H, m), 3.12-3.16 (3H, m), 3.40-4.00 (2H, m), 4.45-4.55 (1H, m), 5.25-5.43 (1H, m), 7.18-7.42 (3H, m), 7.50-7.59 (1H, m), 7.62-7.77 (1H, m), 7.90-8.08 (3H, m), 8.24-8.32 (1H, m), 8.75-8.81 (1H, 1).

ESI-MS(m/e): 493 (M+H).

#### Example 330

Trans-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using cis-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone, the title compound was obtained as a pale yellow solid by the same process as in Example 327, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.70-2.73 (5H, m), 3.11-3.37 (3H, m), 3.62-4.51 (2H, m), 5.24-5.45 (2H, m), 7.13-7.76 (5H, m), 7.94-8.00 (3H, m), 8.28-8.33 (1H, m), 8.73-8.79 (1H, m).

ESI-MS(m/e): 495 (M+H).

#### Example 331

1-(4-oxo-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Dimethylsulfoxide 0.003 ml was added to a solution of oxalyl chloride 0.003ml in chloroform 1 ml at -50°C, and the reaction liquor was stirred at the same temperature for five minutes. A solution of trans-1-(4-hydroxy-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 326, 6.7 mg in chloroform 1 ml was added to the reaction liquor, and thereafter the reaction liquor was stirred at -50°C for 15 minutes. Triethylamine 0.02 ml was added, and the reaction liquor was stirred at room temperature for five minutes, and thereafter the reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The

solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CtC (YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The title compound was obtained as a white solid by eliminating the solvent by distillation under reduced pressure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 2.03 (3H, s), 2.68 (2H, s), 3.16 (3H, s), 4.09-4.22 (2H, m), 5.70-5.77 (1H, m), 7.05-7.80 (5H, m), 7.94-8.01 (3H, m), 8.24-8.32 (1H, m), 8.72-8.77 (1H, m).

ESI-MS(m/e): 491 (M+H).

### Example 332

#### 1-(4,4-difluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

##### Step 1

##### Synthesis of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4,4-difluoro-pyrrolidine

Dimethylsulfoxide 0.035 ml was added to a solution of oxalyl chloride 0.035ml in chloroform 3 ml, at -50°C, and the reaction liquor was stirred at the same temperature for five minutes. A solution of 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4-hydroxy-pyrrolidine 40 mg obtained in Example 325 (Step 3) in chloroform 2 ml was added to the reaction liquor, and thereafter the reaction liquor was stirred at 50°C for ten minutes. Triethylamine 0.10 ml was added, and the reaction liquor was stirred at room temperature for five minutes, and thereafter the reaction liquor was diluted with ethyl acetate, and it was washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and bis (2-methoxyethyl) amino sulphur trifluoride 0.06 ml was added to solution of the obtained residue in chloroform 1 ml, and the reaction liquor was stirred overnight at 70°C. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained.

##### Step 2

##### Production of 1-(4,4-difluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-acetyl-2-(2-fluoro-4-nitro-phenyl)-4,4-difluoro-pyrrolidine obtained in (Step 1), the title compound was obtained as a white solid by the process of Example 325 (Step 4)-(Step 6), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 2.03 (3H x 1/2, s), 2.05 (3H x 1/2, s), 2.50-2.63 (1H, m), 2.85-3.15 (1H, m), 3.14 (3H x 1/2, s), 3.15 (3H x 1/2, s), 3.95-4.25 (2H, m), 5.44-5.58 (1H, m), 7.22-7.29 (2H,

m), 7.26-7.42 (1H, m), 7.48-7.54 (1H, m), 7.61-7.68 (1H, m), 7.94-8.04 (3H, m), 8.26-8.32 (1H, m), 8.72-8.77 (1H, m).

ESI-MS(m/e): 513 (M+H).

#### Example 333

Cis-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

Racemic cis-1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 327 45 mg was optically resolved on optical resolution column (CHIRALPAK AD 2cm phi x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: hexane/2-propanol 30/70, flow rate 10 ml/min), and enantiomer A (retention time = 18 min), enantiomer B (retention time = 22 min) were respectively obtained as white-color solids.

Enantiomer A

ESI-MS(m/e): 495 (M+H).

Enantiomer B.

ESI-MS(m/e): 495 (M+H).

#### Example 334

6-(6-(1-acetyl-pyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazol-2-yl)-nicotinic acid methyl ester

Using pyridine-2,5-dicarboxylic acid-5-methyl ester, the title compound was obtained as yellow solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR/ (CDCl<sub>3</sub>) δ : 1.20-2.40 (7H, m), 2.80-3.20 (3H, m), 3.40-4.00 (2H, m), 3.99 (3H, s), 5.05-5.45 (1H, m), 6.80-7.80 (4H, m), 7.80-8.05 (2H, m), 8.35-8.60 (2H, m), 9.10-9.30 (1H, m), 10.60-11.30 (1H, m).

ESI-MS(m/e): 535 (M+H).

#### Example 335

6-(6-(1-acetyl-pyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazol-2-yl)-nicotinic acid

Using 6-(6-(1-acetyl-pyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazol-2-yl)-nicotinic acid methyl ester obtained in Example 334, the title compound was obtained as pale yellow solid by same process as Example 121 (Step 6), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.60-2.60 (7H, m), 3.21 (3H, s), 3.60-4.00 (2H, m), 5.00-5.20 (1H, m), 6.90-7.60 (4H, m), 7.80-8.00 (2H, m), 8.30-8.60 (2H, m), 9.20 (1H, s).

ESI-MS(m/e): 521 (M+H).

#### Example 336

##### 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid dimethyl amide

###### Step 1

##### Synthesis of 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-2,3-dihydro-1H- benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid 4-nitro-phenyl ester

Triethylamine 0.060 ml and 4-nitrobenzoyl chloride 21 mg were added successively to tetrahydrofuran 1 ml solution of 5-(4-methanesulphonyl-phenoxy)-2- pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B 37mg obtained in Example 163, and the reaction liquor was stirred overnight at room temperature. Reaction solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as a white solid.

###### Step 2

##### Production of 2-(6-(4-methanesulphonyl-phenoxy)-2- pyridin-2-yl-3H- benzimidazol-5-yl)- pyrrolidine-1-carboxylic acid dimethyl amide

Dimethylamine (2.0M tetrahydrofuran solution) 1 ml was added to tetrahydrofuran 1 ml solution of 2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl- 2,3-dihydro-1H-benzimidazol-5-yl)-pyrrolidine-1-carboxylic acid 4-nitro-phenyl ester 20 mg, and the reaction liquor was stirred overnight at 100°C in sealed tube. Reaction solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid). The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate.

By eliminating the solvent under reduced pressure, the title compound was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.80-1.92 (2H, m), 1.94-2.07 (1H, m), 2.33-2.42 (1H, m), 2.80 and 2.85 (total 6H, each brs), 3.12 (3H, s), 3.52-3.58 (1H, m), 3.62-3.78 (1H, m), 5.19-5.26 (1H, m), 7.16-7.80 (5H, m), 7.91-7.99 (3H, m), 8.27 (1H, d, J = 7.6 Hz), 8.73 (1H, brs).

ESI-MS(m/e): 506 (M+H).

**Example 337**1-(2-(2-(6-hydroxy-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-hydroxy-pyridine-2-carboxylic acid, the title compound was obtained as yellow solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.75-2.47 (7H, m), 2.97-3.26 (4H, m), 3.44-3.96 (2H, m), 5.20-5.40 (1H, m), 6.60-8.05 (10H, m).

ESI-MS(m/e): 493 (M+H).

**Example 338**1-(2-(6-(4-fluoro-phenylsulphanyl)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone**Step 1**Synthesis of 2-(4-amino-2-fluoro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester

1-(t-butoxy carbonyl) pyrrole-2-boron acid 1.6 g, tetrakis triphenylphosphine palladium 200 mg, saturated sodium carbonate aqueous solution 5 ml and water 5 ml were added successively to a solution of 4-bromo-3-fluoro-phenylamine 1 g in dimethoxyethane 1 ml, and the reaction liquor was stirred at 70°C for three hours under a nitrogen atmosphere. After cooling, the reaction liquor was filtered with celite, and the filtrate was diluted with ethyl acetate and washed successively with water and saturated aqueous sodium chloride solution and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1) and the title compound was obtained as pale-brown solid.

**Step 2**Synthesis of 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester.

Water 5 ml, 5 % platinum-carbon catalyst 660 mg were added to a solution of 2-(4-amino-2-fluoro-phenyl)-pyrrole-1-carboxylic acid t-butyl ester 2.2g in 2-propanol 50 ml, and, under hydrogen pressure atmosphere of 50 kgf/cm<sup>2</sup>, it was stirred at 50°C for one day. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained as brown oily substance.

**Step 3**Synthesis of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-3-fluoro-phenyl)-amide

Pyridine-2-carboxylic acid 90 mg, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide



monohydrochloride 190 mg were added successively to solution of 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 181 mg in pyridine 2 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was diluted with chloroform, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and 4N hydrochloric acid-dioxane solution 2 ml were added to the obtained residue 300 mg, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with chloroform, and it was made basic with saturated aqueous sodium bicarbonate, then the organic layer was washed using saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and acetic anhydride 0.020 ml was added to pyridine 1 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for 20 minutes. The reaction liquor was diluted with chloroform, and it was washed successively with water and saturated aqueous sodium chloride solution, then dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 50/1) and the title compound was obtained as yellow solid.

#### Step 4

##### Synthesis of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-5-fluoro-2-nitro-phenyl)-amide

Potassium nitrate 94 mg was added to solution of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-3-fluoro-phenyl)-amide in trifluoroacetic acid 3 ml, and the reaction liquor was stirred at room temperature for two days. The reaction liquor was concentrated down by distillation under reduced pressure, then diluted with chloroform, made basic with saturated aqueous sodium bicarbonate. Then extraction was carried out with chloroform. The organic layers were combined and were washed with saturated aqueous sodium chloride solution and were dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 50/1) and the title compound was obtained as a pale yellow solid.

#### Step 5

##### Production of 1-(2-(6-(4-fluoro-phenyl sulphanyl)-2-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

4-fluoro-benzene thiol 20 mg, potassium carbonate 30 mg were added successively to solution of pyridine-2-carboxylic acid-(4-(1-acetyl-pyrrolidin-2-yl)-5-fluoro-2-nitro-phenyl)-amide 50 mg in N,N-dimethylformamide 1 ml, and the reaction liquor was stirred at 100°C for two hours. Tin (II)

chloride dihydrate 30 mg was added to the reaction liquor, and the reaction liquor was stirred at 100°C for a further three hours. After cooling, the reaction liquor was diluted using saturated aqueous sodium bicarbonate, extracted with chloroform, and the organic layer were dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. It was refined by preparative thin layer chromatography and the title compound was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.50 (7H, m), 3.60-4.00 (2H, m), 5.20-5.80 (1H, m), 6.90-7.10 (2H, m), 7.15-7.80 (5H, m), 7.80-8.00 (1H, m), 8.30-8.45 (1H, m), 8.55-8.70 (1H, m), 10.60-11.20 (1H, m).

ESI-MS(m/e): 433 (M+H).

#### Example 339

##### 1-(2-(6-(4-methanesulphonyl-phenyl)sulphonyl)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-methanesulphonyl-benzene thiol, the title compound was obtained as a white solid by same process as Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-2.45 (7H, m), 2.80-3.20 (3H, m), 3.50-4.00 (2H, m), 5.20-5.65 (1H, m), 7.10-8.25 (8H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m), 10.60-11.40 (1H, m).

ESI-MS(m/e): 493 (M+H).

#### Example 340

##### N-(5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide

##### Step 1

##### Synthesis of 1-(2-(6-(6-amino-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

5-bromo-2-nitro-pyridine 53.5 mg, cesium carbonate 84.2 mg, copper (II) oxide 25 mg were added to a solution of 1-(2-(6-hydroxy-2-pyridin-2-yl-3-(2-trimethyl silanyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone obtained in Example 121 (Step 10) 55.0 mg in pyridine 1 ml, and the reaction liquor was stirred overnight at 120°C in sealed tube. After cooling, saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution were added successively to the reaction liquor, extraction was carried out ethyl acetate and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and hydrazine monohydrate 0.016 ml, expanded Raney nickel catalyst 20 mg were added to solution of the obtained residue in ethanol 2 ml, and the reaction liquor was stirred at room temperature for 30 minutes. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced

pressure. The obtained residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1) and the title compound was obtained as a yellow oily substance.

## Step 2

### Production of N-(5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl)-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-acetamide

Acetic anhydride 0.005 ml was added to a solution of 1-(2-(6-(6-amino-pyridin-3-yloxy)-2-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 13.7 mg in pyridine 1 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor concentrated down by distillation under reduced pressure, and the obtained residue was dissolved in trifluoroacetic acid 1 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was concentrated down by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (YMC Co) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid) and silica gel column chromatography (eluent: chloroform / methanol = 9/1) and the title compound was obtained as an oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.64-2.44 (10H, m), 3.57-3.91 (2H, m), 5.26-5.62 (1H, m), 6.76-8.74 (10H, m), 10.59-11.31 (1H, m).

ESI-MS(m/e): 457 (M+H).

## Example 341

### 1-(2-(6-(6-acetyl-pyridin-3-yloxy)-2-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 1-(5-bromo-pyridin-2-yl)-ethanone, the title compound was obtained as an oily substance by the same process as in Example 122, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.66-2.42 (7H, m), 2.59-2.74 (3H, m), 3.51-3.90 (2H, m), 5.12-5.45 (1H, m), 6.85-8.10 (6H, m), 8.30-8.70 (3H, m), 10.86-11.24 (1H, m).

ESI-MS(m/e): 442 (M+H).

## Example 342

### 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl)-1H-benzimidazole enantiomer A and enantiomer B

Racemic 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl)-1H-benzimidazole 100 mg obtained in Example 306 was optically-resolved on optical resolution column (CHIRALPAK AD 2cm phi x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: hexane/isopropanol/diethylamine 20/80/0.1, flow rate 10 ml/min), and enantiomer A (retention

time = 24 min), enantiomer B (retention time = 27 min) were respectively obtained as oily substance.

#### Example 343

1-(2-(2-[5-bromo-pyridin-2-yl]-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A

Acetic anhydride 0.020 ml was added to solution of 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer A (obtained in Example 342) 43mg in pyridine 1 ml, and the reaction liquor was stirred at room temperature for ten minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, it was extracted with chloroform, and the organic layer was dried with anhydrous magnesium sulphate and the solvent was eliminated by distillation under reduced pressure. It was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as a white solid. <sup>1</sup>H-NMR (CDC13) δ : 1.60-2.40 (7H, m), 2.80-3.20 (3H, m), 3.50-3.95 (2H, m), 5.05-5.45 (1H, m), 6.90-7.80 (5H, m), 7.80-8.00 (2H, m), 8.10-8.30 (1H, m), 8.60-8.80 (1H, m). ESI/MS(m/e): 555, 557 (M+H).

#### Example 344

1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer B

Using 2-(5-bromo-pyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-6-pyrrolidin-2-yl-1H-benzimidazole enantiomer B obtained in Example 342, the title compound was obtained as a white solid by the same process as in Example 343, a process based on this or a combination of these with a normal procedure.

#### Example 345

1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(5-vinyl-pyridin-2-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-vinyl-pyridine-2-carboxylic acid, the title compound was obtained as yellow solid by the same process as in Example 307, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.40 (7H, m), 2.90-3.15 (3H, m), 3.50-3.90 (2H, m), 5.00-5.45 (1H, m), 5.48 (1H, dd, J = 5.6, 11.2 Hz), 5.94 (1H, dd, J = 5.6, 17.6 Hz), 6.70-6.85 (1H, m), 7.00-7.25 (2H, m), 7.25-7.80 (2H, m), 7.80-8.00 (3H, m), 8.30-8.40 (1H, m), 8.55-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS(m/e): 503 (M+H).

**Example 346**

1-(2-(6-(6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Methylolithium (1.0M diethyl ether solution) 0.1 ml was added to solution of 1-(2-(6-(6-acetyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 341) 15.0 mg in tetrahydrofuran 1.5 ml solution at -78°C, and the reaction liquor was stirred at -78°C for 30 minutes. The reaction liquor was discharged into saturated ammonium chloride aqueous solution, extracted with chloroform and the extract was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: chloroform-methanol = 7.5/1) and the title compound was obtained as yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.46-1.63 (6H, m), 1.63-2.47 (7H, m), 2.87-2.99 and 3.34-3.91 (total 3H, each m), 5.18-5.51 (1H, m), 6.72-7.91 (6H, m), 8.17-8.68 (3H, m), 10.54-10.94 (1H, br).

ESI-MS(m/e): 458 (M+H).

**Example 347**

(5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-carbamic acid ethyl ester

Ethyl chloroformate 0.003ml was added to solution of 1-(2-(6-(6-amino-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone (obtained in Example 340 (Step 1) 14.4 mg in pyridine 1 ml, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was concentrated down by distillation under reduced pressure, and the obtained residue was dissolved in trifluoroacetic acid 1 ml, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was concentrated down by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography (ODS-AS-360-CC (YMC Co) mobile phase : water-acetonitrile-0.1% trifluoroacetic acid) and silica gel column chromatography (eluent: chloroform-methanol = 9/1) and the title compound was obtained as a yellow oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.14-1.51 (3H, m), 1.52-2.46 (7H, m), 2.78-2.93 and 3.51-3.88 (total 3H, each m), 4.16-4.26 (2H, m), 5.27-5.63 (1H, m), 6.80-8.69 (10H, m).

ESI-MS(m/e): 487 (M+H).

**Example 348**

1-(2-(6-(6-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 5-bromo-2-cyano-pyridine, the title compound was obtained as a white solid by the same process as in Example 153, a process based on this or a combination of these with a normal

procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.49-2.42 (7H, m), 2.54-2.71 (3H, m), 3.50-3.88 (2H, m), 5.04-5.48 (1H, m), 7.00-8.67 (10H, m).

ESI-MS(m/e): 482 (M+H).

#### Example 349

3-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-3-oxo-propionitrile

Using cyanoacetic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.80-2.05 (4H, m), 3.05-3.25 (4H, m), 3.47-3.93 (3H, m), 5.19-5.41 (1H, m), 7.00-7.59 (5H, m), 7.82-7.99 (3H, m), 8.35-8.41 (1H, m), 8.62-8.68 (1H, m).

ESI-MS(m/e): 502 (M+H).

#### Example 350

Cyclopropyl-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-methanone

Using cyclopropanecarboxylic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.92-1.108 (4H, m), 1.60-1.66 (2H, m), 1.85-1.99 (2H, m), 2.20-2.38 (1H, m), 3.05-3.08 (3H, m), 3.63-4.00 (2H, m), 5.33-5.41 (1H, m), 7.12-7.44 (5H, m), 7.86-7.92 (3H, m), 8.40-8.44 (1H, m), 8.60-8.68 (1H, m).

ESI-MS(m/e): 503 (M+H).

#### Example 351

3,3,3-trifluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-propan-1-one

Using 3,3,3-trifluoro-propionic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.85-2.40 (4H, m), 2.90-3.27 (5H, m), 3.65-3.90 (2H, m), 5.15-5.43 (1H, m), 6.97-7.63 (5H, m), 7.84-7.96 (3H, m), 8.38-8.43 (1H, m), 8.60-8.68 (1H, m).

ESI-MS(m/e): 545 (M+H).

#### Example 352

(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-(tetrahydrofuran-2-yl)-methanone

Using tetrahydrofuran-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.85-2.33 (7H, m), 3.05-3.10 (3H, m), 3.63-4.08 (5H, m), 4.15-4.62 (1H, m), 5.33-5.62 (1H, m), 7.11-7.55 (5H, m), 7.84-7.95 (3H, m), 8.37-8.42 (1H, m), 8.60-8.67 (1H, m).

ESI-MS(m/e): 533 (M+H).

#### Example 353

N-(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-acetamide

Using acetylaminocetic acid, the title compound was obtained as a white solid by the same process as in Example 296, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.90-2.05 (8H, m), 3.07-3.09 (3H, m), 3.47-4.01 (3H, m), 5.16-5.40 (1H, m), 6.52-6.70 (1H, m), 7.04-7.20 (2H, m), 7.33-7.57 (2H, m), 7.84-7.98 (3H, m), 8.35-8.38 (1H, m), 8.61-8.67 (1H, m).

ESI-MS(m/e): 534 (M+H).

#### Example 354 (diastereomer A), 355 (diastereomer B)

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer A and diastereomer B

Using 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14 and 1-pyrrolidin-2-yl-ethanol, the title compound was obtained as diastereomer mixture of pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure. The obtained diastereomer mixture was purified further by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1), diastereomer A and B were respectively obtained as pale yellow solid.

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer A.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.09 (3H, d, J = 6.7 Hz), 1.66-1.78 (1H, m), 1.80-1.99 (3H, m), 3.06-3.18 (1H, m), 3.12 (3H, s), 3.61-3.69 (1H, m), 3.78-3.83 (1H, m), 3.90-3.99 (1H, m), 6.97-7.81 (5H, m), 7.89-8.00 (3H, m), 8.26 (1H, d, J = 8.2 Hz), 8.74 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 479 (M+H).

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-et

anol diastereomer B.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 0.76 (3H, d, J = 6.3 Hz), 1.70-1.82 (3H, m), 1.92-2.00 (1H, m), 3.06-3.13 (1H, m), 3.10 (3H, s), 3.61-3.69 (1H, m), 3.83-3.90 (1H, m), 3.95-4.03 (1H, m), 7.04 (2H, d, J = 8.9 Hz), 7.37-7.44 (2H, m), 7.46-7.49 (1H, m), 7.89 (2H, d, J = 8.9 Hz), 7.93-7.99 (1H, m), 8.27 (1H, d, J = 7.8), 8.74 (1H, d, J = 4.7 Hz)

ESI-MS(m/e) : 479 [M+H]

**Example 356**5-(2-(1-fluoro-ethyl)-pyrrolidin-1-yl)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To solution of 1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer A 21mg obtained in Example 354 in chloroform 1 ml was added diethylamino sulphur trifluoride 0.007 ml at -78°C, and the reaction liquor was stirred at 78°C for one hour. The reaction liquor was warmed to room temperature and thereafter, saturated aqueous sodium bicarbonate was added to the reaction liquor and thereafter, it was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as pale yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.18 and 1.24 (total 3H, each d, J = 6.3, 6.7 Hz), 1.53-1.78 (1H, m), 1.83-2.00 (3H, m), 3.11 (3H, s), 3.11-3.20 (1H, m), 3.52-3.61 (1H, m), 3.89-4.01 (1H, m), 4.63-4.87 (1H, m), 7.04 (2H, d, J = 9.0 Hz), 7.21-7.53 (3H, m), 7.89 (2H, d, J = 9.0 Hz), 7.96-8.02 (1H, m), 8.27 (1H, d, J = 7.8 Hz), 8.74 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 481 (M+H).

**Example 357**5-(2-(1-fluoro-ethyl)-pyrrolidin-1-yl)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol diastereomer B obtained in Example 355, the title compound was obtained as a pale yellow solid by the same process as in Example 356, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 0.99 and 1.09 (total 3H, each d, J = 6.5, 6.2 Hz), 1.59-1.83 (3H, m), 1.93-2.03 (1H, m), 3.00-3.10 (1H, m), 3.09 (3H, s), 3.54-3.67 (1H, m), 4.10-4.19 (1H, m), 4.37-4.54 (1H, m), 7.04 (2H, d, J = 8.9 Hz), 7.36-7.48 (3H, m), 7.86 (2H, d, J = 8.9 Hz), 7.94-7.98 (1H, m), 8.25 (1H, d, J = 7.8 Hz), 8.72 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 481 (M+H).



**Example 358**1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Oxalyl chloride 0.080 ml and dimethylsulfoxide 0.087 ml were added successively at -78°C to methylene chloride 3 ml, and the reaction liquor was stirred at 78°C for ten minutes, and thereafter, solution of diastereomer mixture of 1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanol (obtained in Example 354 and 355) 146 mg in methylene chloride 2 ml was added at -78°C. The reaction liquor was stirred at -78°C for 30 minutes, and thereafter, triethylamine 0.42 ml was added, and the reaction liquor was stirred at -78°C for a further ten minutes, and thereafter, it was warmed to room temperature. Saturated ammonium chloride aqueous solution was added to the reaction liquor, and the mixture was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (KieselgelTM60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound was obtained as pale yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.78-2.07 (3H, m), 1.94 (3H, s), 2.20-2.29 (1H, m), 3.06 (3H, s), 3.37-3.45 (1H, m), 3.64-3.77 (1H, m), 4.27-4.30 (1H, m), 6.80-7.44 (5H, m), 7.80-7.88 (3H, m), 8.27-8.40 (1H, m), 8.61-8.62 (1H, m).

ESI-MS(m/e): 477 (M+H).

**Example 359 (enantiomer A), 360 (enantiomer B)**1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A and enantiomer B

Racemic

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone (obtained in Example 358) 27 mg was optically resolved on optical resolution column (CHIRALPAK AD-H 2cm φ x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: ethanol, flow rate 10 ml/min), and enantiomer A (retention time = 20.8 min), enantiomer B (retention time = 46.9 min) were respectively obtained as pale yellow solids.

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A.

ESI-MS(m/e): 477 (M+H).

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer B.

ESI-MS(m/e): 477 (M+H).

**Example 361**1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 5-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-2-nitro-phenylamine obtained from Example 196 (Step 3) and 1-methyl-1-(2-pyrrolidinyl) ethanol, the title compound was obtained as pale yellow solid by the same process as in Example 354, 355 and 358, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.80-2.10 (3H, m), 2.08 (3H, s), 2.28-2.39 (1H, m), 3.24 (3H, s), 3.40-3.47 (1H, m), 3.66-3.73 (1H, m), 4.46 (1H, t, J = 7.4 Hz), 7.17 (1H, s), 7.40 (1H, s), 7.48 (1H, dd, J = 2.7, 8.8 Hz), 7.54 (1H, dd, J = 4.9, 7.6 Hz), 8.02 (1H, dt, J = 0.8, 7.8 Hz), 8.07 (1H, dd, J = 0.6, 8.8 Hz), 8.24 (1H, d, J = 7.8 Hz), 8.46 (1H, dd, J = 0.6, 2.7 Hz), 7.78 (1H, dt, J = 0.8, 4.9 Hz).

ESI-MS(m/e): 478 (M+H)

**Example 362 (enantiomer A), 363 (enantiomer B)**1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A and enantiomer B

Racemic 1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone obtained in Example 361 34 mg was optically resolved on optical resolution column (CHIRALPAK AD-H 2cm  $\phi$  x 25 cm L (Diacel Chemical Industries, Ltd.), moving phase: ethanol, flow rate 10 ml/min), and enantiomer A (retention time = 28.8 min), enantiomer B (retention time = 48.2 min) were respectively obtained as pale yellow solids.

1-(1-(6-[6-methanesulphonyl-pyridin-3-yloxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer A.

ESI-MS(m/e): 478 (M+H).

1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone enantiomer B

ESI-MS(m/e): 478 (M+H).

**Example 364**(2S)-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using L-prolinamide hydrochloride and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these

with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.91-2.03 (3H, m), 2.26-2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18-3.28 (1H, m), 3.63-3.91 (1H, m), 4.19-4.23 (1H, m), 6.04-6.13 (1H, m), 6.86-7.28 (4H, m), 7.37-7.41 (1H, m), 7.48-7.54 (1H, m), 7.80-7.92 (3H, m), 8.34-8.38 (1H, m), 8.48-8.63 (1H, m).  
ESI-MS(m/e): 478 (M+H).

#### Example 365

##### (2R)-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using D-prolinamide and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.91-2.03 (3H, m), 2.26-2.50 (1H, m), 3.02 and 3.06 (total 3H, each s), 3.18-3.28 (1H, m), 3.63-3.91 (1H, m), 4.19-4.23 (1H, m), 6.04-6.13 (1H, m), 6.86-7.28 (4H, m), 7.37-7.41 (1H, m), 7.48-7.54 (1H, m), 7.80-7.92 (3H, m), 8.34-8.38 (1H, m), 8.48-8.63 (1H, m).  
ESI-MS(m/e): 478 (M+H).

#### Example 366

##### 6-((3R)-3-fluoro-pyrrolidin-1-yl)-5-(4-methanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using (R)-3-fluoro pyrrolidine and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a yellow oily substance by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.95-2.40 (2H, m), 3.10 (3H, s), 3.25-3.73 (4H, m), 5.14-5.40 (1H, m), 7.06 (2H, d, J = 8.9 Hz), 7.07-7.20 (1H, m), 7.32-7.40 (1H, m), 7.42-7.48 (1H, m), 7.89 (2H, d, J = 8.9 Hz), 7.93-7.99 (1H, m), 8.23 (1H, d, J = 8.2 Hz), 8.71 (1H, d, J = 5.1 Hz)  
ESI-MS(m/e): 453 (M+H).

#### Example 367

##### 1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-3-carboxamide

Using pyrrolidine-3-carboxamide and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.03-2.30 (2H, m), 2.89-2.99 (1H, m), 3.06 (3H, s), 3.24-3.60 (4H, m),

5.70-5.86 (2H, m), 7.00-7.48 (5H, m), 7.80-7.90 (3H, m), 8.34-8.40 (1H, m), 8.57-8.64 (1H, m).  
ESI-MS(m/e): 478 (M+H).

**Example 368**

(2R)-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxylic acid methoxy-methyl-amide

Using (R)-N-methoxy-N-methylprolinamide and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.83-2.05 (3H, m), 2.25-2.40 (1H, m), 3.09 (3H, brs), 3.13 (3H, s), 3.40-3.47 (1H, m), 3.68-3.78 (1H, m), 3.84 (3H, brs), 4.90-5.09 (1H, m), 7.06-7.30 (4H, m), 7.42-7.50 (1H, m), 7.87-8.00 (3H, m), 8.19-8.28 (1H, m), 8.70-8.76 (1H, m).

ESI-MS(m/e): 522 (M+H).

**Example 369**

(2R)-1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(6-ethanesulfonyl-pyridin-3-yloxy)-5-fluoro-2-nitro-phenylamine obtained from Example 221 (Step 2) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as pale yellow solid by the same process as in Example 354, 55 and Example 358, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.4 Hz), 1.78-2.03 (3H, m), 2.03 (3H, s), 2.22-2.35 (1H, m), 3.30-3.43 (1H, m), 3.39 (2H, q, J = 7.4 Hz), 3.64-3.75 (1H, m), 4.35-4.42 (1H, m), 7.03-7.48 (4H, m), 7.90-7.99 (1H, m), 8.03 (1H, d, J = 8.6 Hz), 8.17-8.28 (1H, m), 8.43-8.46 (1H, m), 8.70-8.75 (1H, m).

ESI-MS(m/e): 492 (M+H).

**Example 370**

(2R)-1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(6-ethanesulfonyl-pyridin-3-yloxy)-5-fluoro-2-nitro-phenylamine obtained from Example 225 (Step 2) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as pale yellow solid by the same process as in Example 205 and Example 358, a process based on this or a sequential combination of these with a normal procedure

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.4 Hz), 1.80-2.03 (3H, m), 2.04 (3H, s), 2.24-2.34 (1H, m), 3.30-3.45 (1H, m), 3.39 (2H, q, J = 7.4 Hz), 3.63-3.74 (1H, m), 4.37-4.44 (1H, m), 7.07 (1H, brs), 7.22-7.50 (2H, m), 8.03-8.05 (1H, m), 8.42-8.46 (1H, m), 8.63-8.66 (1H, m), 8.73 (1H, d, J

= 1.6 Hz), 9.37-9.43 (1H, m).

ESI-MS(m/e): 493 (M+H).

#### Example 371

(2R)-1-(1-(6-(4-ethanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(4-ethane sulfonyl-phenoxy)-5-fluoro-2-nitro-phenylamine obtained from Example 259 (Step 1) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 1.81-2.03 (3H, m), 2.02 (3H, s), 2.24-2.33 (1H, m), 3.22 (2H, q, J = 7.4 Hz), 3.38-3.46 (1H, m), 3.72-3.79 (1H, m), 4.40 (1H, t, J = 7.5 Hz), 7.10-7.12 (3H, m), 7.29 (1H, s), 7.45-7.48 (1H, m), 7.87-7.90 (2H, m), 7.90-7.98 (1H, m), 8.24 (1H, d, J = 7.6 Hz), 8.72 (1H, d, J = 4.9 Hz).

ESI-MS(m/e): 491 (M+H).

#### Example 372

(2R)-1-(1-(6-(4-ethane sulfonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone

Using the 4-(4-ethane sulfonyl-phenoxy)-5-fluoro-2-nitro-phenylamine obtained from Example 259 (Step 1) and 1-(R)-pyrrolidin-2-yl-ethanol, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 1.82-2.04 (3H, m), 2.04 (3H, s), 2.24-2.34 (1H, m), 3.22 (2H, q, J = 7.4 Hz), 3.34-3.50 (1H, m), 3.70-3.79 (1H, m), 4.38-4.48 (1H, m), 7.00-7.38 (4H, m), 7.89 (2H, d, J = 9.0 Hz), 8.66 (1H, brs), 8.75 (1H, dd, J = 1.6, 2.5 Hz), 9.38-9.48 (1H, m).

ESI-MS(m/e): 492 (M+H).

#### Example 373

(2R)-1-(1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-propan-1-one

Using 5-fluoro-4-(6-ethane sulfonyl-pyridin-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and 1-(R)-pyrrolidine-2-yl-propanol, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 0.93 (3H, t, J = 7.2 Hz), 1.25-1.27 (3H, m), 1.75-2.00 (3H, m), 2.23-2.53 (3H, m), 3.33-3.44 (3H, m), 3.71 (2H, q, J = 7.3 Hz), 4.43 (1H, t, J = 7.6 Hz) 7.14 (1H, s), 7.38

(1H, s), 7.45-7.50 (2H, m), 7.93-8.00 (1H, m), 8.06 (1H, d, J = 8.8 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.45 (1H, d, J = 2.9 Hz), 8.73 (1H, d, J = 4.9 Hz).

ESI-MS(m/e): 506 (M+H).

#### Example 374

(2R)-2-(1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-propane-2-ol

Using 5-fluoro-4-(6-ethane sulfonyl-pyridin-3-yloxy)-2-nitro-phenylamine obtained in Example 221 (Step 2) and (R)-1-methyl-1-(2-pyrrolidinyl) ethanol, the title compound was obtained by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 0.85 and 0.87 (total 6H, each s), 1.22 (3H, t, J = 7.3 Hz), 1.59-1.84 (3H, m), 1.93-2.05 (1H, m), 3.08-3.17 (1H, m), 3.31-3.40 (2H, m), 3.53-3.61 (1H, m), 4.00-4.03 (1H, m), 7.43-7.64 (4H, m), 7.91-7.98 (1H, m), 8.02 (1H, d, J = 8.8 Hz), 8.25 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 2.7 Hz), 8.71-8.73 (1H, m).

ESI-MS(m/e): 508 (M+H).

#### Example 375

(2R, 4R)-4-hydroxy-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using cis-4-hydroxy-D-prolinamide, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.94-2.00 (1H, m), 2.50-2.59 (1H, m), 3.11 (3H, s), 3.38-3.44 (1H, m), 3.73-3.77 (1H, m), 4.23-4.28 (1H, m), 4.36-4.42 (1H, m), 7.12 (2H, d, J = 9.0 Hz), 7.24 (1H, s), 7.33 (1H, s), 7.44-7.47 (1H, m), 7.89-7.97 (3H, m), 8.21-8.24 (1H, m), 8.70-8.72 (1H, m).

ESI-MS(m/e): 494 (M+H).

#### Example 376

(2R, 4S)-4-fluoro-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using (2R, 4R)-4-hydroxy-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide obtained in Example 375, the title compound was obtained as a pale yellow solid by the same process as in Example 356, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 2.01-2.21 (1H, m), 2.54-2.67 (1H, m), 3.13 (3H, s), 3.48 (1H, dd, J = 12.8, 27.2 Hz), 4.09 (1H, ddd, 3.6, 12.8, 39.7 Hz = J), 4.48 (1H, dd, J = 6.4, 10.0 Hz), 5.20-5.34 (1H, m), 7.15 (2H, d, J = 8.8 Hz), 7.25 (1H, brs), 7.41 (1H, brs), 7.46-7.49 (1H, m), 7.92-7.99 (3H, m),

8.26 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 4.7 Hz).

**Example 377**

(2R, 4S)-4-hydroxy-1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-2-carboxamide

Using trans-4-hydroxy-D-prolinamide, the title compound was obtained as a pale yellow solid by the same process as in Example 15, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 2.00-2.07 (1H, m), 2.33-2.39 (1H, m), 3.13 (3H, s), 3.25 (1H, d, J = 10.8 Hz), 4.00 (1H, dd, J = 4.1, 10.8 Hz), 4.44-4.50 (2H, m), 7.14 (2H, d, J = 9.0 Hz), 7.23 (1H, brs), 7.37 (1H, brs), 7.46-7.49 (1H, m), 7.92-7.99 (3H, m), 8.25 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 4.7 Hz).

ESI-MS(m/e): 494 (M+H).

**Example 378**

1-((2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidin-2-yl)-ethanone

**Step 1**

Synthesis of (2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl-amide

Using (2R, 4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide obtained in Reference Example 5, the title compound was obtained as a pale yellow solid by the same process as in Example 369, a process based on this or a combination of these with a normal procedure.

**Step 2**

Production of 1-((2R,4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidin-2-yl)-ethanone

Methylolithium (1.0M diethyl ether solution) 0.360 ml was added to a solution of 20 mg of the (2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl-amide obtained in step 1 in tetrahydrofuran 1 ml, at -78°C. The reaction liquor was stirred at -78°C for one hour and thereafter, it was warmed to 0°C and was stirred for one hour. Saturated ammonium chloride aqueous solution was added to the reaction liquor, and the mixture was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the residue obtained was purified by preparative thin layer chromatography (Kieselgel<sup>TM</sup>60F254, Art5744 (Merck Corporation), chloroform/methanol = 10/1) and the title compound as pale yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 7.4 Hz), 1.79-1.88 (1H, m), 2.08 (3H, s), 2.43-2.54 (1H, m), 3.33 (2H, q, J = 7.4 Hz), 3.46-3.63 (2H, m), 4.34-4.43 (2H, m), 7.10 (1H, brs), 7.39 (1H, brs), 7.43-7.50 (2H, m), 7.93-7.97 (1H, m), 8.04 (1H, d, J = 8.8 Hz), 8.23 (1H, d, J = 8.0 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.71 (1H, d, J = 4.3 Hz).

ESI-MS(m/e): 508 (M+H).

#### Example 379

1-((2R, 4S)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrrolidin-2-yl)-ethanone.

Using the 1-((2R, 4R)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-4-hydroxy-pyrrolidin-2-yl)-ethanone obtained in Example 378, the title compound was obtained as pale yellow solid by the same method as in Example 356, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.31 (3H, t, J = 7.4 Hz), 1.80-2.05 (1H, m), 1.96 and 2.02 (total 3H, each s), 2.26-2.60 (1H, m), 3.30-3.43 (2H, m), 3.43-3.66 (1H, m), 3.70-4.04 (1H, m), 4.50-4.64 (1H, m), 5.12-5.37 (1H, m), 6.90-7.56 (4H, m), 7.80-7.91 (1H, m), 7.93-8.02 (1H, m), 8.30-8.68 (3H, m).

ESI-MS(m/e): 510 (M+H).

#### Example 380

1-((2R, 4S)-1-(6-(6-ethane sulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrrolidin-2-yl)-ethanone

Using (2R, 4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide obtained in Reference Example 5, the title compound was obtained as pale yellow solid by the same process as in Example 370 and Example 378 (Step 2) and Example 356, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.25 (3H, t, J = 7.4 Hz), 1.98-2.20 (1H, m), 2.05 (3H, s), 2.48-2.61 (1H, m), 3.41 (2H, q, J = 7.4 Hz), 3.56 (1H, dd, J = 11.9, 24.5 Hz), 3.99 (1H, ddd, J = 3.1, 11.9, 39.1 Hz), 4.65 (1H, dd, J = 6.6, 10.3 Hz), 5.22-5.36 (1H, m), 7.13 (1H, brs), 7.48-7.50 (2H, m), 8.05 (1H, dd, J = 0.6, 8.8 Hz), 8.52 (1H, d, J = 2.8 Hz), 8.67 (1H, d, J = 2.5 Hz), 8.76 (1H, dd, J = 1.4, 2.5 Hz), 9.43 (1H, d, J = 1.4 Hz)

ESI-MS(m/e): 511 (M+H).

#### Example 381

5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 2-fluorophenol and 5-fluoro-4-(4-methanesulphonyl-phenoxy)-2-nitro-phenylamine obtained in Example 14, the title compound was obtained as a colourless solid by same process as Example (Step 4)-(Step 6), by a process based on this or a combination of these with a normal



procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.10 (3H, s), 6.98-7.05-(1H, m), 7.07-7.21 (5H, m), 7.21-7.66 (3H, m), 7.88 (2H, d, J = 9.0 Hz), 7.98 (1H, t, J = 7.6 Hz), 8.28 (1H, d, J = 8.2 Hz), 8.74 (1H, s).

ESI-MS(m/e): 476 (M+H).

#### Example 382

##### 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-(4-methanesulphonyl-phenoxy)-4-(2-fluoro-phenoxy)-benzene-1,2-diamine obtained in Example 381, the title compound was obtained as a brown solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.11 (3H, s), 7.00-7.08 (1H, m), 7.08-7.70 (5H, m), 7.11 (2H, d, J = 8.8 Hz), 7.90 (2H, d, J = 8.8 Hz), 8.71 (1H, s), 8.78 (1H, s), 9.47 (1H, s).

ESI-MS(m/e): 477 (M+H).

#### Example 383

##### 5-(2,3-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,3-difluoro phenol, the title compound was obtained as pale yellow solid by same process as Example 196, (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.20 (3H, s), 6.79-6.83 (1H, m), 6.98-7.12 (2H, m), 7.17-7.80 (4H, m), 7.98-8.05 (2H, m), 8.27-8.35 (1H, m), 8.39 (1H, d, J = 2.7 Hz), 8.64-8.79 (1H, m).

ESI-MS(m/e): 495 (M+H).

#### Example 384

##### 5-(2,4-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,4-difluoro phenol, the title compound was obtained as pale yellow solid by same process as Example 196 (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.21 (3H, s), 6.91-7.41 (4H, m), 7.47-7.75 (3H, m), 7.98-8.06 (2H, m), 8.27-8.33 (1H, m), 8.40-8.45 (1H, m), 8.66-8.76 (1H, m).

ESI-MS(m/e): 495 (M+H).

#### Example 385

##### 5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,5-difluoro phenol, the title compound was obtained as pale yellow solid by same process

as Example 196 (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.20 (3H, s), 6.85-6.95 (2H, m), 7.24 (1H, td, J = 9.6, 5.1 Hz), 7.53 (1H, s), 7.56 (1H, dd, J = 8.6, 2.7 Hz), 7.64 (1H, dd, J = 7.8, 4.7 Hz), 7.81 (1H, s), 8.05 (1H, d, J = 8.6 Hz), 8.10 (1H, t, J = 7.8 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.43 (1H, d, J = 2.7 Hz), 8.84 (1H, d, J = 4.7 Hz)

ESI-MS(m/e): 495 (M+H).

#### Example 386

##### 5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2,6-difluoro phenol, the title compound was obtained as pale yellow solid by same process as Example 196 (Step 4)-(Step 6), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.22 (3H, s), 7.09-7.17 (2H, m), 7.14 (2H, t, J = 8.2 Hz), 7.26-7.32 (1H, m), 7.47-7.52 (1H, m), 7.55 (1H, dd, J = 9.0, 2.3 Hz), 7.98 (1H, t, J = 7.8 Hz), 8.07 (1H, d, J = 9.0 Hz), 8.27 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.72-8.74 (1H, m).

ESI-MS(m/e): 495 (M+H).

#### Example 387

##### 5-(2,5-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 4-(2,5-difluoro-phenoxy)-5-(6-methanesulphonyl-pyridin-3-yloxy)-benzene-1,2 -diamine obtained in Example 385, the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.21 (3H, s), 6.75-6.92 (2H, m), 7.17-7.24 (1H, m), 7.35-7.85 (2H, m), 7.52 (1H, dd, J = 8.6, 2.7 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.41 (1H, d, J = 2.7 Hz), 8.73 (1H, s), 8.79 (1H, s), 9.50 (1H, s).

ESI-MS(m/e): 496 (M+H).

#### Example 388

##### 5-(3,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 3,4-difluoro phenol, the title compound was obtained as pale yellow solid by the same process as in Example 383 and Example 387, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  : 3.18 (3H, s), 6.65 (1H, brs), 6.80 (1H, brs), 7.17 (1H, q, J = 9.4 Hz), 7.46

(1H, dd, J = 8.6, 2.7 Hz), 7.49-7.80 (2H, m), 8.00 (1H, d, J = 8.6 Hz), 8.33 (1H, d, J = 2.7 Hz), 8.6.9 (1H, s), 8.76 (1H, s), 9.46 (1H, s).

ESI-MS(m/e): 496 (M+H).

#### Example 389

5-(3,5-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 3,5-difluoro phenol, the title compound was obtained as a pale yellow solid by the same process as in Example 388, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.22 (3H, s), 6.41-6.49 (2H, m), 6.60-6.69 (1H, m), 7.50 (1H, dd, J = 8.6, 2.7 Hz), 7.54-7.82 (2H, m), 8.04 (1H, d, J = 8.6 Hz), 8.36 (1H, d, J = 2.7 Hz), 8.74 (1H, brs), 8.80 (1H, brs), 9.52 (1H, s).

ESI-MS(m/e): 496 (M+H).

#### Example 390

5-(2-difluoromethoxypyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(5-methyl-pyrazin-2-yl)-1H-benzimidazole

Using 5-methyl-pyrazine-2-carboxylic acid and 4-(2-difluoromethoxy-pyridin-3-yloxy)-5-(6-methanesulphonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 215, the title compound was obtained as a pale yellow solid by the same process as in Example 38, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 2.65 (3H, s), 3.18 (3H, s), 7.15 (1H, dd, J = 8.0, 4.9 Hz), 7.32-7.80 (2H, m), 7.40 (1H, d, J = 7.4 Hz), 7.45 (1H, dd, J = 8.8, 2.7 Hz), 7.46 (1H, t, J = 72.6 Hz), 7.93 (1H, dd, J = 4.9, 1.4 Hz), 8.01 (1H, dd, J = 8.8, 0.6 Hz), 8.35 (1H, dd, J = 2.7, 0.6 Hz), 8.67 (1H, d, J = 1.0 Hz), 9.32 (1H, d, J = 1.3 Hz)

ESI-MS(m/e): 541 (M+H).

#### Example 391

5-phenoxy-2-pyrazin-2-yl-6-(6-ethane sulfonyl-pyridin-3-yloxy)-1H-benzimidazole

##### Step 1

Synthesis of pyrazine-2-carboxylic acid (5-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide

Pyrazine-2-carboxylic acid 3.18 g, 1-hydroxybenzotriazole 4.1 g and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydrochloride 5.8 g were added to a solution of the 3-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-phenylamine obtained in Example 221 (Step 1) 7.5 g dissolved in dimethylformamide 7 ml, the reaction liquor was stirred overnight at room temperature. Water was added to the reaction liquor, and precipitate was

recovered by filtration, to give 8.0g crude product. Fuming nitric acid 0.44 ml was added to a solution of the obtained crude product 3.6g in trifluoroacetic acid 35 ml, and the reaction liquor was stirred at room temperature overnight, and thereafter the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and, precipitate was recovered by filtration, to give the title compound.

## Step 2

### Production of 5-(2,5-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole

2,5-difluoro-phenol 15 mg and cesium carbonate 28 mg were added to a solution of pyrazine-2-carboxylic acid (5-fluoro-4-(6-methanesulphonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide obtained in (Step 1) 26 mg in N-methylpyrrolidinone 0.5 ml, and the reaction liquor was stirred at 90°C for 15 minutes, and thereafter, tin (II) chloride dihydrate 100 mg was added to the reaction liquor. The reaction liquor was stirred at 90°C for one hour, and thereafter, ethyl acetate and saturated aqueous sodium bicarbonate were added. The precipitate was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a pale yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.23 (3H, t, J = 7.2 Hz), 3.24-3.44 (2H, m), 6.82-6.92 (2H, m), 7.04-7.18 (1H, m), 7.26-7.38 (3H, m), 7.48-7.56 (2H, m), 8.03 (1H, d, J = 8.4 Hz), 8.38 (1H, s), 8.74 (1H, s), 8.81 (1H, s), 9.51 (1H, s).

ESI-MS(m/e): 474 (M+H).

## Example 392

### 5-(naphthalen-1-yl

### oxy)-2-pyrazine-2-yl-6-(6-ethanesulfonyl-pyridine-3-yloxy)-1H-benzimidazole

Using naphthalene-1-ol and pyrazine-2-carboxylic acid (5-fluoro-4-(6-ethanesulfonyl-pyridine-3-yloxy)-2-nitro-phenyl)-amide obtained in Example 391, the title compound was obtained as a brown solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.17 (3H, t, J = 7.4 Hz), 3.29 (2H, q, J = 7.4 Hz), 6.81 (1H, d, J = 7.6 Hz), 7.29-7.40 (3H, m), 7.45-7.49 (1H, m), 7.55 (1H, d, J = 7.6 Hz), 7.56 (1H, s), 7.72 (1H, d, J = 8.6 Hz), 7.75 (1H, s), 7.83 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 8.6 Hz), 8.17 (1H, d, J = 3.0 Hz), 8.70 (1H, dd, J = 2.3, 1.2 Hz), 8.77 (1H, d, J = 2.3 Hz), 9.48 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 524 (M+H).

#### Example 393

5-(naphthalen-2-yl oxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using naphthalene-2-ol and pyrazine-2-carboxylic acid (5-fluoro-4-(6-ethanesulfonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide obtained in Example 391, the title compound was obtained as a brown solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure..

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.11 (3H, t, J = 7.6 Hz), 3.24 (2H, q, J = 7.6 Hz), 7.10 (1H, dd, J = 8.8, 2.5 Hz), 7.16 (1H, brs), 7.35-7.46 (3H, m), 7.50 (1H, d, J = 3.1 Hz), 7.52 (1H, d, J = 2.5 Hz), 7.67 (1H, d, J = 8.2 Hz), 7.81 (1H, s), 7.83 (1H, s), 7.95 (1H, d, J = 6.3 Hz), 8.34 (1H, d, J = 2.3 Hz), 8.73 (1H, d, J = 2.7 Hz), 8.80 (1H, dd, J = 2.7, 1.6 Hz), 9.52 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 524 (M+H).

#### Example 394

5-(2-difluoromethyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-difluoromethyl-phenol, the title compound was obtained as a colourless solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.21 (3H, t, J = 8.4 Hz), 3.37 (2H, q, J = 8.4 Hz), 6.72 (1H, t, J = 59.8 Hz), 6.85-6.90 (1H, m), 7.17 (1H, t, J = 8.6 Hz), 7.39-7.46 (3H, m), 7.51-7.84 (3H, m), 7.98-8.05 (2H, m), 8.31-8.39 (2H, m), 8.65-8.85 (1H, m).

ESI-MS (m/e): 523 (M+H).

#### Example 395

5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 196, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.3 Hz), 3.37 (2H, q, J = 7.3 Hz), 6.88 (1H, d, J = 8.2 Hz), 7.16 (1H, t, J = 7.4 Hz), 7.40-7.46 (2H, m), 7.51-7.54 (1H, m), 7.64 (1H, brs), 7.70 (1H, brs), 7.87 (1H, d, J = 7.8 Hz), 7.98 (1H, d, J = 8.6 Hz), 8.01 (1H, t, J = 8.6 Hz), 8.30 (1H, d, J = 2.7 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.76 (1H, brs).

ESI-MS (m/e): 516 (M+H).

**Example 396**5-benzyloxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 4-benzyloxy-3-fluoroaniline obtained in Example 250 (Step 1), picolinic acid and 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained as a brown solid by the same process as in Example 250, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.26 (3H, t, J = 7.6 Hz), 3.35 (2H, q, J = 7.6 Hz), 5.07 (2H, s), 7-10-7.13 (2H, m), 7.15 (1H, s), 7.26-7.27 (4H, m), 7.34-7.39 (1H, m), 7.51 (1Hx1/2, s), 7.64 (1Hx1/2, s), 7.83-7.86 (1H, m), 7.95-7.96 (1H, m), 8.33-8.35 (1H, m), 8.45-8.46 (1H, m), 8.60-8.63 (1H, m), 10.43-10.46 (1H, m).

ESI-MS (m/e): 487 (M+H).

**Example 397**5-(2-methanesulphonyl-6-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole**Step 1**Synthesis of 5-hydroxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-benzyloxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 396, the title compound was obtained as pale green colored solid by the same process as in Example 251 (Step 1), a process based on this or a combination of these with a normal procedure.

**Step 2**Production of 5-(2-methanesulphonyl-6-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-hydroxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in (Step 1) and 1,2-difluoro-3-methanesulphonyl-benzene, the title compound was obtained as pale green colored solid by the same process as in Example 251, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 2.97 (3H, s), 3.41 (2H, q, J = 7.4 Hz), 7.11 (1H, s), 7.50-7.57 (2H, m), 7.61-7.70 (2H, m), 7.70 (1H, s), 7.87 (1H, d, J = 8.0 Hz), 7.99 (1H, t, J = 8.0 Hz), 8.10 (1H, d, J = 8.6 Hz), 8.27 (1H, d, J = 7.0 Hz), 8.57 (1H, d, J = 2.7 Hz), 8.74 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 569 (M+H).

**Example 398**5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 1,2-difluoro-3-cyano-benzene and 5-hydroxy-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 397, the title compound was obtained as pale green colored solid by the same process as in Example 251, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.26 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.27-7.43 (1H, m), 7.40 (1H, td, J = 8.0, 4.6 Hz), 7.49-7.55 (2H, m), 7.56-7.76 (3H, m), 7.99 (1H, t, J = 7.6 Hz), 8.06 (1H, d, J = 9.0 Hz), 8.30 (1H, d, J = 7.6 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.75 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 516 (M+H).

#### Example 399

##### 5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl- 6-(6-ethanesulfonyl -pyridin-3-yloxy)-1H-benzimidazole obtained in Example 397, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD),  $\delta$  : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.00-7.18 (1H, m), 7.34-7.43 (2H, m), 7.49 (1H, brs), 7.54-7.56 (2H, m), 7.66 (1H, brs), 7.97 (1H, t, J = 8.0 Hz), 8.07 (1H, d, J = 8.6 Hz), 8.20-8.30 (1H, m), 8.53 (1H, d, J = 2.7 Hz), 8.70-8.77 (1H, m).

ESI-MS (m/e): 534 (M+H).

#### Example 400

##### 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

###### Step 1

###### Synthesis of 3-fluoro-4-(2-fluoro-6-cyano-phenoxy)-phenylamine

Using (3-fluoro-4-hydroxy-phenyl)-carbamic acid tert-butyl ester obtained in Example 196 (Step 1) and 1,2-difluoro-3-cyano-benzene, the title compound was obtained by the same process as in Example 221 (Step 1), a process based on this or a combination of these with a normal procedure.

###### Step 2

###### Synthesis of pyrazine-2-carboxylic acid (5-fluoro-4-(2-fluoro-6-cyano-phenoxy)-2-nitro-phenyl)-amide

Using 5-fluoro-4-(2-fluoro-6-cyano-phenoxy)-phenylamine obtained in (Step 1) and pyrazine-2-carboxylic acid, the title compound was obtained by the same process as in Example 391 (Step 1), a process based on this or a combination of these with a normal procedure.

###### Step 3

###### Production of 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H

-benzimidazole

Using pyrazine-2-carboxylic acid (5-fluoro-4-(2-fluoro-6-cyano-phenoxy)-2-nitro-phenyl)- amide obtained in (Step 2) and 4-ethanesulphonyl-phenol, the title compound was obtained as a brown solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 7.4 Hz), 3.20 (2H, q, J = 7.4 Hz), 7.12 (2H, d, J = 9.0 Hz), 7.33-7.40 (2H, m), 7.55-7.62 (3H, m), 7.86 (2H, d, J = 9.0 Hz), 8.72 (1H, s), 8.78 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 516 (M+H).

**Example 401**

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole and 5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole obtained in Example 400, the title compounds were obtained as brown solid and pale yellow solid respectively by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.25 (3H, t, J = 7.4 Hz), 3.22 (2H, q, J = 7.4 Hz), 7.00-7.34 (1H, m), 7.23 (2H, d, J = 8.8 Hz), 7.34-7.70 (4H, m), 7.91 (2H, d, J = 8.8 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.46 (1H, s).

ESI-MS (m/e): 534 (M+H).

5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.10 (6H, d, J = 9.6 Hz), 1.24 (3H, t, J = 7.4 Hz), 3.01-3.11 (2H, m), 4.06-4.16 (1H, m), 6.80-7.87 (9H, m), 8.52-8.60 (2H, m), 9.51-9.54 (1H, m), 10.78-10.80 (1H, m).

ESI-MS (m/e): 576 (M+H).

**Example 402**

5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using pyrazine-2-carboxylic acid (5-fluoro-4-(2-cyano-6-fluoro-phenoxy)-2-nitro-phenyl)-amide obtained in Example 400 (Step 2) and 6-ethanesulfonyl-pyridin-3-ol, the title compound was



obtained as a white solid by the same process as in Example 400 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$  : 1.10 (3H, t, J = 7.4 Hz), 3.27-3.36 (2H, m), 7.22-7.35 (1H, m), 7.38-7.50 (2H, m), 7.72-7.77 (3H, m), 7.98 (1H, d, J = 9.0 Hz), 8.50 (1H, d, J = 2.7 Hz), 8.76 (1H, s), 8.79 (1H, s), 9.45 (1H, s).

ESI-MS (m/e): 517 (M+H).

#### Example 403

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole and

5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin -3-yloxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole obtained in Example 402, the title compound was obtained as a colourless solid by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.27 (3H, t, J = 7.4 Hz), 3.43 (2H, q, J = 7.4 Hz), 7.08-7.11 (1H, m), 7.38-7.46 (2H, m), 7.46-7.80 (3H, m), 8.10 (1H, d, J = 4.7 Hz), 8.55 (1H, d, J = 2.7 Hz), 8.71 (1H, s), 8.78 (1H, s), 9.47 (1H, s).

ESI-MS (m/e): 535 (M+H).

5-(2-fluoro-6-isopropyl carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.08 (6H, d, J = 6.6 Hz), 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.94-4.02 (1H, m), 7.10 (1H, s), 7.36-7.46 (3H, m), 7.59 (1H, d, J = 9.0 Hz), 7.74 (1H, s), 8.08 (1H, d, J = 9.0 Hz), 8.56 (1H, s), 8.75 (1H, s), 8.80 (1H, s), 9.44 (1H, s).

ESI-MS (m/e): 577 (M+H).

#### Example 404

5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin -3-yloxy)-1H-benzimidazole obtained in Example 402, the title compound was obtained as a colourless solid by the same process as in Example 60, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.27 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.37-7.46 (4H, m), 7.60 (1H, s), 7.84 (1H, d, J = 5.9 Hz), 7.94 (1H, d, J = 9.0 Hz), 8.32 (1H, d, J = 2.0 Hz), 8.71 (1H, s), 8.77 (1H, s), 9.47 (1H, s).

ESI-MS (m/e): 560 (M+H).

#### Example 405

5-(2-methyl sulphanyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-methylsulphanyl-phenol, the title compound was obtained as pale yellow solid by the same process as in Example 221 (Step 3), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.28 (3H, t, J = 7.4 Hz), 3.38 (2H, q, J = 7.4 Hz), 6.78 (1H, ddd, J = 7.6, 7.6, 1.5 Hz), 7.03-7.12 (2H, m), 7.08 (1/2H, s), 7.16 (1H, d, J = 7.6 Hz), 7.30 (1H, dd, J = 8-7, 2.5 Hz), 7.36 (1/2H, s), 7.37-7.41 (1H, m), 7.47 (1/2H, s), 7.72 (1/2H, s), 7.86-7.90 (1H, m), 7.97 (1H, d, J = 8.7 Hz), 8.38 (1H, d, J = 2.5 Hz), 8.38-8.41 (1H, m), 8.61-8.63 (1H, m), 11.16 (1/2H, brs), 11.28 (1/2H, brs).

ESI-MS (m/e): 519 (M+H).

#### Example 406

5-(2-methane sulphinyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole and 5-(2-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

To methanol 3 ml solution of 5-(2-methyl sulphanyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole 46 mg obtained in Example 405 were added water 2 ml and oxone 89 mg, and thereafter the reaction liquor was stirred at room temperature for five hours. The solvent was eliminated by distillation under reduced pressure, and thereafter, the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 15/1), and obtained the title compound as pale yellow solid.

5-(2-methane sulphinyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.30 (3H, t, J = 7.6 Hz), 2.59 (3/2H, s), 2.63 (3/2H, s), 3.38 (2H, q, J = 7.6 Hz), 6.78-6.81 (1H, m), 7.25-7.33 (2H, m), 7.35-7.43 (1H, m), 7.08 (1/2H, s), 7.16 (1H, d, J = 7.6 Hz), 7.30 (1H, dd, J = 8.7, 2.5 Hz), 7.36 (1/2H, s), 7.37-7.41 (1H, m), 7.47 (1/2H, s), 7.72 (1/2H, s), 7.86-7.90 (1H, m), 7.97 (1H, d, J = 8.7 Hz), 8.38 (1H, d, J = 2.5 Hz), 8.38-8.41 (1H, m), 8.61-8.63 (1H, m), 11.16 (1/2H, brs), 11.28 (1/2H, brs).

ESI-MS (m/e): 535 (M+H).

5-(2-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 2.95 (3/2H, s), 3.02 (3/2H, s), 3.36 (2H, q, J = 7.4 Hz), 6.92-6.97 (1H, d), 7.20-7.27 (1H, m), 7.31-7.35 (3/2H, m), 7.41-7.45 (3/2H, m), 7.51-7.57 (1H, m), 7.65 (1/2H, s), 7.72 (1/2H, s), 7.87-7.92 (1H, m), 7.97-8.04 (2H, m), 8.34-8.42 (2H, m), 8.65-8.67 (1H, m), 10.72 (1H, brs).

ESI-MS (m/e): 551 (M+H).

**Example 407**

5-(2-bromopyridin-3-yloxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-bromo-pyridin-3-ol and pyrazine-2-carboxylic acid (5-fluoro-4-(6-ethanesulfonyl-pyridin-3-yloxy)-2-nitro-phenyl)-amide obtained in Example 391, the title compound was obtained as pale yellow solid by the same process as in Example 391, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.03 (1H, dd, J = 8.0, 1.6 Hz), 7.19-7.22 (1H, m), 7.28-7.32 (1H, m), 7.34 (1/2H, brs), 7.51 (1/2H, brs), 7.62 (1/2H, brs), 7.93 (1/2H, brs), 8.00 (1H, d, J = 8.6 Hz), 8.14 (1H, brs), 8.31-8.32 (1H, m), 8.62 (1H, brs), 8.70 (1H, d, J = 2.4 Hz), 9.64 (1H, brs), 10.91 (1/2H, brs), 10.98 (1/2H, brs).

ESI-MS (m/e): 553 (M+H).

**Example 408**

5-(2-vinyl

pyridin-3-yloxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using 2-vinyl-pyridin-3-ol, the title compound was obtained as a pale yellow solid by the same process as in Example 407, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.27 (3H, t, J = 7.5 Hz), 3.37 (2H, q, J = 7.5 Hz), 5.34 (1H, dd, J = 10.9, 1.9 Hz), 6.30 (1H, dd, J = 17.4, 1.9 Hz), 6.72 (1H, dd, J = 17.4, 10.9 Hz), 7.09 (1H, dd, J = 8.2, 1.5 Hz), 7.12 (1H, dd, J = 8.2, 4.3 Hz), 7.27 (1H, dd, J = 8.7, 2.9 Hz), 8.00 (1H, d, J = 8.7 Hz), 8.31 (1H, d, J = 2.9 Hz), 8.33 (1H, dd, J = 4.3, 1.5 Hz), 8.61 (1H, dd, J = 2.6, 1-6 Hz), 8.69 (1H, d, J = 2.6 Hz), 10.60 (1/2H, brs), 10.68 (1/2H, brs).

ESI-MS (m/e): 501 (M+H).

**Example 409**

5-(2-cyclopropyl-pyridin-3-yloxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzi

imidazole

Using 2-cyclopropyl-pyridin-3-ol, the title compound was obtained as a pale yellow solid by the same process as in Example 407, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.77-1.02 (2H, m), 1.24-1.31 (2H, m), 1.29 (3H, t, J = 7.4 Hz), 3.37 (2H, q, J = 7.4 Hz), 6.96 (2/5H, dd, J = 8.2, 4.6 Hz), 6.98 (3/5H, dd, J = 8.2, 4.6 Hz), 7.03 (2/5H, dd, J = 8.2, 1.5 Hz), 7.04 (3/5H, dd, J = 8.2, 1.5 Hz), 7.16 (1/2H, s), 7.33 (1H, dd, J = 8.8, 3.0 Hz), 7.48 (1/2H, s), 7.53 (1/2H, s), 7.78 (1/2H, s), 8.00 (1H, d, J = 8.8 Hz), 8.20 (2/5H, dd, J = 4.6, 1-5 Hz), 8.22 (3/5H, dd, J = 4.6, 1.5 Hz), 8.39 (2/5H, d, J = 3.0 Hz), 8.40 (3/5H, d, J = 3.0 Hz), 8.59-8.62 (1H, m), 8.68-8.70 (1H, m), 9.62-9.64 (1H, m), 10.60 (3/5H, brs), 10.66 (2/5H, brs).

ESI-MS (m/e): 515 (M+H).

**Example 410**5-(2-difluoromethoxypyridin-3-yloxy)-2-pyridin-2-yl-6-(4-dimethylsulphamoyl-phenoxy)-1H-benzimidazole

4-(N,N-dimethylamino sulfonyl)-phenol and 2-difluoromethoxy-pyridin-3-ol were successively used, and, by the same process as in Example 221 (Step 1)-(Step 3), a process based on these or a combination of these with a normal procedure, the title compound was obtained as pale yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 2.66 (6H, s), 7.05 (2H, d, J = 8.6 Hz), 7.10-7.19 (1H, m), 7.32-7.62 (4H, m), 7.49 (1H, t, J = 72.8 Hz), 7.71 (2H, d, J = 8.6 Hz), 7.91 (1H, d, J = 4.1 Hz), 8.01 (1H, t, J = 7.8 Hz), 8.32 (1H, d, J = 7.6 Hz), 8.77 (1H, s).

ESI-MS (m/e): 554 (M+H).

**Example 411**5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

4-methanesulphonyl-3-chloro-phenol and 2-difluoromethoxy-pyridin-3-ol were successively used, and, by the same process as in Example 221 (Step 1)-(Step 3), a process based on these or a combination of these with a normal procedure, the title compound was obtained as pale yellow solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.25 (3H, s), 6.98 (1H, dd, J = 8.6, 2.3 Hz), 7.09 (1H, d, J = 2.3 Hz), 7.15 (1H, dd, J = 7.8, 4.9 Hz), 7.35-7.46 (2H, m), 7.46-7.74 (3H, m), 7.48 (1H, t, J = 74.0 Hz), 7.91-7.94 (1H, m), 8.02 (1H, d, J = 8.6 Hz), 8.32 (1H, d, J = 7.8 Hz), 8.75-8.77 (1H, m).

ESI-MS (m/e): 552 (M-H).

**Example 412**5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-(N-hydroxycarbamimidoyl)-phenoxy)-1H-

benzimidazole

To ethanol 0.5 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-cyano-pyridin-3-yloxy)-1H-benzimidazole 6.0 mg obtained in Example 252 was added hydroxyamine (50 % aqueous solution) 0.5 ml, and the reaction liquor was stirred at room temperature for three hours. Thereafter the title compound was obtained as pale yellow solid by eliminating the solvent under reduced pressure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 7.01-7.04 (1H, m), 7.10-7.22 (3H, m), 7.29-7.35 (2H, m), 7.60 (1H, s), 7.82 (1H, d, J = 9.0 Hz), 8.24 (1H, d, J = 2.3 Hz), 8.70 (1H, d, J = 1.6 Hz), 8.77 (1H, d, J = 1.6 Hz), 9.48 (1H, s).

ESI-MS (m/e): 458 (M+H).

**Example 413**5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-(5-methyl-[1,2,4]oxadiazole)-3-yloxy)-1H-benzimidazole

Acetic anhydride 1 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-(N-hydroxycarbamimidoyl)-phenoxy)-1H-benzimidazole 3.6 mg obtained in Example 412 was stirred overnight at 60°C. The solvent was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. The solvent (sic) of the obtained fraction was diluted with ethyl acetate and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a colourless solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 2.69 (3H, s), 7.00-7.40 (5H, m), 7.48 (1H, dd, J = 7.8, 2.3 Hz), 7.52-7.85 (1H, m), 8.10 (1H, d, J = 7.8 Hz), 8.37 (1H, d, J = 2.3 Hz), 8.71 (1H, s), 8.78 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 482 (M+H).

**Example 414**5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-(5-trifluoromethyl-[1,2,4]oxadiazole)-3-yloxy)-1H-benzimidazole

Anhydrous trifluoroacetic acid 1 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(4-(N-hydroxycarbamimidoyl)-phenoxy)-1H-benzimidazole 2.0 mg obtained in Example 412 was stirred at 60°C for one hour. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 15/1), and the title compound was obtained as a colourless solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 7.00-7.50 (5H, m), 7.55 (1H, dd, J = 7.8 Hz, 2.3 Hz), 7.60-7.80 (1H, m),

8.22 (1H, d, J = 7.8 Hz), 8.45 (1H, d, J = 2.3 Hz), 8.73 (1H, s), 8.80 (1H, s), 9.50 (1H, s).

ESI-MS (m/e): 536 (M+H).

#### Example 415

5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(imidazo [1,2-a] pyridine-6-yloxy)-1H -benzimidazole

##### Step 1

Synthesis of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-nitro-pyridin-3-yloxy)-1H -benzimidazole

Using 2-nitro-5-pyridine, the title compound was obtained by the same process as in Example 251 (Step 2), a process based on these or a combination of these with a normal procedure.

##### Step 2

Production of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(imidazo [1,2-a] pyridine-6-yloxy) -1H-benzimidazole

To methanol 0.5 ml solution of 5-(2-fluoro-phenoxy)-2-pyrazin-2-yl-6-(6-nitro-pyridin-3-yloxy)-1H-benzimidazole 12 mg obtained in (Step 1), expanded Raney nickel catalyst was added, and the reaction liquor was stirred under a hydrogen atmosphere for one hour. The catalyst was eliminated by filtration, and next the solvent was eliminated by distillation under reduced pressure. To ethanol 0.3 ml solution of the obtained residue, chloroacetaldehyde (40 % aqueous solution) 0.02 ml was added, and thereafter the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, then the residue was purified by preparative thin layer chromatography (Kieselgel TM60F254, Art5744 (Merck Co.), chloroform/methanol = 15/1) and the title compound was obtained as pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.25 (3H, t, J = 7.0 Hz), 3.73 (2H, q, J = 7.0 Hz), 7.00-7.22 (6H, m), 7.31-7.65 (4H, m), 7.82 (1/2H, s), 7.88 (1/2H, s), 8.57 (1H, dd, J = 2.5, 1.5 Hz), 8.64 (1H, s), 9.59 (1H, s), 10.57 (1/2H, brs), 10.97 (1/2H, brs).

ESI-MS (m/e): 439 (M+H).

#### Example 416

5-(pyridin-2-yl sulphanyl)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole

Using pyridine-2-thiol, the title compound was obtained as yellow solid by the same process as in Example 391 (Step 1), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.23 (3H, t, J= 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 7.07 (1H, d, J = 8.2 Hz), 7.11 (1H, dd, J = 7.4, 4.9 Hz), 7.41 (1H, d, J = 7.6 Hz), 7.58-7.80 (1H, m), 7.60 (1H, td, J = 7.6, 1.8 Hz), 7.95 (1H, dd, J = 8.6, 0.6 Hz), 8.00-8.25 (1H, m), 8.28 (1H, dd, J = 5.1, 1.0 Hz), 8.33 (1H, d, J = 0.6 Hz), 8.75 (1H, d, J = 2.5 Hz), 8.82 (1H, dd, J = 2.5, 1.5 Hz), 9.53 (1H, d, J = 1.5 Hz).

ESI-MS (m/e): 491 (M+H).

**Example 417****5-(3-cyano-pyridin-2-yl sulphanyl)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole**

Using 3-cyano-pyridine-2-thiol, the title compound was obtained as yellow solid by the same process as in Example 391 (Step 2), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.29 (3H, t, J = 7.4 Hz), 3.36 (2H, q, J = 7.4 Hz), 7.08 (1H, dd, J = 7.8, 4.9 Hz), 7.35 (1H, dd, J = 8.6, 2.8 Hz), 7.35 and 7.65 (total 1H, each s), 7.80 (1H, dd, J = 7.8, 1.8 Hz), 7.93 (1H, d, J = 8.4 Hz), 7.95 and 8.22 (total 1H, each s), 8.36 (2H, d, J = 2.5 Hz), 8.63 (1H, s), 8.71 (1H, s), 9.65 (1H, d, J = 1.4 Hz).

ESI-MS (m/e): 516 (M+H).

**Example 418****5-(2-chlorophenyl-sulphanyl)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole**

Using 2-chloro-thiophenol, the title compound was obtained as pale yellow solid by the same process as in Example 196 (Step 4)-(Step 6), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.20 (3H, s), 7.03-7.10 (1H, m), 7.13-7.20 (2H, m), 7.34-7.39 (2H, m), 7.50-7.86 (3H, m), 7.94 (1H, d, J = 8.6 Hz), 8.01 (1H, t, J = 7.8 Hz), 8.29-8.35 (2H, m), 8.77 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 509 (M+H).

**Example 419****4-(2-cyano-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H- benzimidazole**

2-cyano-phenol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.78 (1H, s), 7.12 (1H, d, J = 8.6 Hz), 7.29-7.31 (2H, m), 7.50-7.51 (1H, m), 7.63-7.65 (2H, m), 7.82 (1H, d, J = 7.4 Hz), 7.9-5-7.97 (1H, m), 8.08 (1H, d, J = 8.6 Hz), 8.32 (1H, d, J = 8.2 Hz), 8.55 (1H, d, J = 2.7 Hz), 8.75 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 498 (M+H).

**Example 420****4-(2-cyano-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H- benzimidazole**

Using 3-(2-cyano-phenoxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 419, the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.27 (3H, t, J = 8.0 Hz), 3.42 (2H, q, J = 8.0 Hz), 6.79-6.84 (1H, m), 7.14-7.17 (1H, m), 7.31-7.35 (1H, m), 7.61-7.68 (2H, m), 7.80-7.85 (2H, m), 8.08 (1H, d, J = 8.4 Hz), 8.54-8.59 (1H, m), 8.70-8.73 (1H, m), 8.77-8.79 (1H, m), 9.48-9.50 (1H, m).

ESI-MS (m/e): 499 (M+H).

#### Example 421

##### 4-(2-cyano-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-cyano-phenoxy)-5-(6-methanesulphonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 286, the title compound was obtained as a white solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.24 (3H, s), 6.80-6.83 (1H, m), 7.72 (1H, q, J = 8.6 Hz), 7.30-7.50 (2H, m), 7.60-7.80 (2H, m), 7.88 (1H, d, J = 7.8 Hz), 8.11 (1H, d, J = 9.0 Hz), 8.56 (1H, s), 8.73 (1H, s), 8.79 (1H, s), 9.50 (1H, 1).

ESI-MS (m/e): 485 (M+H).

#### Example 422

##### 4-(2,3-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2,3-difluoro-phenol and 6-methanesulphonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.23 (3H, s), 6.70 (1H, d, J = 2.3 Hz), 7.12-7.25 (3H, m), 7.29 (1H, d, J = 2.3 Hz), 7.60-7.65 (2H, m), 8.07-8.10 (2H, m), 8.39 (1H, d, J = 7.9 Hz), 8.50 (1H, d, J = 3.4 Hz), 8.83-8.85 (1H, m).

ESI-MS (m/e): 495 (M+H).

#### Example 423

##### 4-(2,3-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 3-(2,3-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 285, the title compound was obtained by the same process as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.6 Hz), 3.40 (2H, q, J = 7.6 Hz), 6.71 (1H, d, J = 2.0 Hz), 7.12-7.26 (3H, m), 7.30 (1H, d, J = 2.0 Hz), 7.60-7.68 (2H, m), 8.06-8.13 (2H, m), 8.40 (1H,



d, J = 7.4 Hz), 8.52 (1H, d, J = 2.7 Hz), 8.86 (1H, d, J = 5.1 Hz).

ESI-MS (m/e): 509 (M+H).

#### Example 424

##### 4-(2,5-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

2,5-difluoro-phenol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 8.2 Hz), 3.41 (2H, q, J = 8.2 Hz), 6.59 (1H, s), 6.99-7.05 (1H, m), 7.06-7.14 (1H, m), 7.22 (1H, br, s), 7.34 (1H, td, J = 9.8, 4.9 Hz), 7.61 (1H, dd, J = 8.6, 4.3 Hz), 8.07 (1H, d, J = 8.6 Hz), 8.52, (1H, d, J = 4.3 Hz), 8.72 (1H, d, J = 1.2 Hz), 8.79 (1H, s), 9.54 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 510 (M+H).

#### Example 425

##### 4-(2,5-difluoro-phenoxy)-6-(6-ethansulphonyl-pyridine-3-yloxy)-2-pyridine-2-yl-1H-benzimidazole

Using 3-(2,5-difluoro-phenoxy)-5-(6-ethanesulfonyl-pyridine-3-yloxy)-benzene-1,2-diamine obtained in Example 424, the title compound was obtained as a white solid by the same process as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.5 Hz), 3.40 (2H, q, J = 7.5 Hz), 6.55 (1H, s), 6.96-7.05 (1H, m), 7.05-7.14 (1H, m), 7.21 (1H, s), 7.28-7.38 (1H, m), 7.50-7.56 (1H, m), 7.56-7.63 (1H, m), 7.97-8.03 (1H, m), 8.07 (1H, d, J = 8.2 Hz), 8.38 (1H, d, J = 7.0 Hz), 8.51 (1H, s), 8.76 (1H, s).

ESI-MS (m/e): 509 (M+H).

#### Example 426

##### 4-(2,6-difluoro-phenoxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole

2,6-difluoro-phenol and 4-ethansulphonyl phenol were successively used, and, by the same process as in Example 278, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 6.37 (1H, brs), 7.13-7.25 (5H, m), 7.34-7.39 (1H, m), 7.89 (2H, d, J = 8.8 Hz), 8.78 (1H, d, J = 2.7 Hz), 8.84 (1H, dd, J = 1.6, 2.7 Hz), 9.56 (1H, d, J = 1.6 Hz)

ESI-MS (m/e): 509 (M+H).

#### Example 427

4-(2,6-difluoro-phenoxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 3-(2,6-difluoro-phenoxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 426, the title compound was obtained by the same process as in Example 204 (Step 2), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 6.23 (1H, brs), 7.08 (1H, brs), 7.15-7.22 (4H, m), 7.28-7.38 (1H, m), 7.51 (1H, t, J = 5.9 Hz), 7.87 (2H, d, J = 9.0 Hz), 8.00 (1H, t, J = 7.4 Hz), 8.41 (1H, d, J = 7.4 Hz), 8.76 (1H, brs).

ESI-MS (m/e): 508 (M+H).

**Example 428**4-(2-difluoromethyl-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

2-difluoromethyl-phenol and 6-ethanesulfonyl-pyridin-3-ol were used successively and the title compound was obtained as a colourless solid by the same process as in Example 274, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.50 (1H, s), 7.15 (1H, d, J = 7.4 Hz), 7.22 (1H, t, J = 55.5 Hz), 7.34 (1H, t, J = 7.4 Hz), 7.49-7.62 (4H, m), 7.74 (1H, d, J = 7.4 Hz), 7.98 (1H, t, J = 7.4 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.37 (1H, d, J = 7.4 Hz), 8.49 (1H, d, J = 2.3 Hz), 8.74-8.77 (1H, m).

ESI-MS (m/e): 523 (M+H).

**Example 429**4-(2-difluoromethyl-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(2-difluoromethyl-phenoxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 428, the title compound was obtained as yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.8 Hz), 3.40 (2H, q, J = 7.8 Hz), 6.54 (1H, s), 7.17 (1H, d, J = 7.4 Hz), 7.21 (1H, t, J = 55.8 Hz), 7.36 (1H, t, J = 7.4 Hz), 7.50-7.65 (2H, m), 7.75 (1H, d, J = 7.4 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.72 (1H, s), 8.79 (1H, s), 9.54 (1H, s).

ESI-MS (m/e): 524 (M+H).

**Example 430**4-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

2-difluoromethoxy-pyridin-3-ol and 4-ethansulphonyl-phenol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.25 (3H, t, J = 7.3 Hz), 3.40 (2H, q, J = 7.3 Hz), 6.60 (1H, d, J = 2.0 Hz), 7.27-7.30 (2H, m), 7.57-7.61 (2H, m), 7.64 (1H, t, J = 72.1 Hz), 7.73 (1H, dd, J = 7.8, 1.6 Hz), 8.05-8.08 (2H, m), 8.10 (1H, dd, J = 4.9, 1.6 Hz), 8.37 (1H, d, J = 8.2 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.81 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 540 (M+H).

#### Example 431

##### 4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole

Using

3-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-5-(4-ethanesulfonyl-phenoxy)-benzene-1,2-diamine obtained in Example 274 (Step 1), the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 7.4 Hz), 3.21 (2H, q, J = 7.4 Hz), 3.65 (3H, s), 6.38 (1H, t, J = 7.2 Hz), 6.44 (1H, s), 7.07 (1H, s), 7.15-7.22 (2H, m), 7.40 (1H, d, J = 7.0 Hz), 7.57 (1H, dd, J = 7.0, 1.8 Hz), 7.84-7.90 (2H, m), 8.70 (1H, s), 8.76 (1H, s), 9.52 (1H, s).

ESI-MS (m/e): 504 (M+H).

#### Example 432

##### 4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

1-methyl-2-oxo-1,2-dihydro-pyridin-3-ol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained as pale-brown solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.65 (5H, s), 6.36 (1H, t, J = 6.7 Hz), 6.46 (1H, s), 7.13 (1H, s), 7.38-7.60 (4H, m), 7.95-8.08 (2H, m), 8.35 (1H, s), 8.49 (1H, s), 8.73 (1H, s).

ESI-MS (m/e): 504 (M+H).

#### Example 433

##### 4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using

3-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 432, the title compound was obtained as a pale yellow solid by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$  : 1.13 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.50 (3H, s), 6.24 (1H,

t, J = 6-8 Hz), 6.46 (1H, s), 7.05 (1H, brs), 7.32-7.40 (1H, m), 7.58 (1H, dd, J = 8.8, 2.5 Hz), 7.74 (1H, dd, J = 6.8, 2.0 Hz), 8.01 (1H, d, J = 8.6 Hz), 8.57 (1H, d, J = 2.5 Hz), 8.79 (1H, d, J = 2.2 Hz), 8.82 (1H, dd, J = 2.5, 1.5 Hz), 9.47 (1H, d, J = 1.4 Hz).

ESI-MS (m/e): 505 (M+H).

#### Example 434

4-(2-cyano-pyridin-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

##### Step 1

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(1-oxy-pyridin-3-yloxy)-phenylamine

Using 1-oxy-pyridin-3-ol and 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 67 (Step 1) and (Step 2), a process based on these or a combination of these with a normal procedure and this.

##### Step 2

Synthesis of 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(2-cyano-pyridin-3-yloxy)-phenylamine

Using 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(1-oxy-pyridin-3-yloxy)-phenylamine, the title compound was obtained by the same process as in Example 218 (Step 2), a process based on this or a combination of these with a normal procedure.

##### Step 3

Production of 4-(2-cyano-pyridin-3-yloxy)-6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 5-(4-methanesulphonyl-phenoxy)-2-nitro-3-(2-cyano-pyridin-3-yloxy)-phenylamine, the title compound was obtained by the same process as in Example 196 (Step 5) and 204 (Step 1), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.23 (3H, s), 7.07 (1H, brs), 7.44 (1H, brs), 7.56-7.69 (4H, m), 8.02 (1H, t, J = 7.8 Hz), 8.09 (1H, d, J = 8.6 Hz), 8.29 (1H, d, J = 7.8 Hz), 8.46-8.48 (1H, m), 8.55-8.57 (1H, m), 8.78-8.80 (1H, m).

ESI-MS (m/e): 485 (M+H).

#### Example 435

4-(2-cyano-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-ethanesulphonyl-phenol, the title compound was obtained by the same process as in Example 434, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.3 Hz), 3.22 (2H, q, J = 7.3 Hz), 6.94 (1H, brs), 7.27 (2H, d, J = 8.6 Hz), 7.33 (1H, brs), 7.49 (2H, d, J = 8.6 Hz), 7.59-7.62 (1H, m), 7.91-7.98 (3H, m), 8.24 (1H, d, J = 8.6 Hz), 8.45 (1H, d, J = 5.1 Hz), 8.74 (1H, d, J = 5.5 Hz)

ESI-MS (m/e): 498 (M+H).

#### Example 436

##### 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Benzyl alcohol and 6-ethanesulfonyl-pyridin-3-ol were successively used, and, by the same process as in Example 274, a process based on this or a combination of these with a normal procedure, the title compound was obtained.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.24 (3H, t, J = 7.6 Hz), 3.45 (2H, q, J = 7.6 Hz), 5.41 (2H, s), 7.02-7.05 (1H, m), 7.15-7.17 (1H, m), 7.39-7.45 (3H, m), 7.53-7.59 (4H, m), 8.07 (1H, d, J = 8.6 Hz), 8.11-8.14 (1H, m), 8.39 (1H, d, J = 7.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.87-8.90 (1H, m).

ESI-MS (m/e): 487 (M+H).

#### Example 437

##### 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-benzyloxy-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2-diamine obtained in Example 436, the title compound was obtained by the same process as in Example 205, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.27 (3H, t, J = 7.4 Hz), 3.42 (2H, q, J = 7.4 Hz), 5.38 (2H, s), 6.80 (1H, d, J = 2.0 Hz), 7.06 (1H, d, J = 2.0 Hz), 7.36-7.42 (3H, m), 7.49 (1H, dd, J = 8.8, 2.9 Hz), 7.54 (2H, d, J = 6.7 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.72 (1H, d, J = 2.7 Hz), 8.78-8.80 (1H, m), 9.54-9.56 (1H, m).

ESI-MS (m/e): 488 (M+H).

#### Example 438

##### 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

##### Step 1

##### Synthesis of 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 436, the title compound was obtained by the same process as in Example 251 (Step 1), by a process based on this or a combination of these with a normal procedure.

##### Step 2

##### Production of 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole and 2,3-difluoro benzonitrile, the title compound was obtained by the same process as in Example 251 (Step 2), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.26 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.61 (1H, d, J = 2.0 Hz), 7.28 (1H, d, J = 2.0 Hz), 7.36-7.42 (1H, m), 7.48-7.54 (1H, m), 7.58-7.63 (2H, m), 7.65-7.69 (1H, m), 8.07 (2H, d, J = 8.2 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 2.7 Hz), 8.82 (1H, d, J = 4.7 Hz).

ESI-MS (m/e): 516 (M+H).

#### Example 439

##### 4-(6-cyano-pyridin-2-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 438 (Step 1) and 2-chloro-3-cyanopyridine, the title compound was obtained by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.26 (3H, t, J = 7.4 Hz), 3.42 (2H, q, J = 7.4 Hz), 7.21 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 7.4, 5.1 Hz), 7.48 (1H, d, J = 2.0 Hz), 7.58 (1H, dd, J = 5.1, 7.8 Hz), 7.71 (1H, dd, J = 8.8, 2.9 Hz), 8.00-8.05 (1H, m), 8.11 (1H, d, J = 8.6 Hz), 8.26-8.33 (3H, m), 8.60 (1H, d, J = 2.7 Hz), 8.78 (1H, d, J = 5.1 Hz).

ESI-MS (m/e): 499 (M+H).

#### Example 440

##### 4-(2-cyano-3-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 2,6-difluoro benzonitrile, the title compound was obtained by the same process as in Example 439, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.26 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.91 (1H, d, J = 8.6 Hz), 7.04 (1H, d, J = 1.8 Hz), 7.13 (1H, t, J = 8.6 Hz), 7.44 (1H, d, J = 1.8 Hz), 7.55-7.64 (2H, m), 7.67 (1H, dd, J = 8.6, 3.2 Hz), 8.00-8.06 (1H, m), 8.10 (1H, d, J = 8.6 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.57 (1H, d, J = 2.3 Hz), 8.78-8.81 (1H, m).

ESI-MS (m/e): 516 (M+H).

#### Example 441

##### 4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 438, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.24 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.53 (1H, brs), 7.26 (1H, brs), 7.42-7.53 (2H, m), 7.57-7.62 (2H, m), 7.68 (1H, dd, J = 8.2, 3.9 Hz), 8.07 (1H, d, J = 8.6

Hz), 8.11-8.16 (1H, m), 8.41 (1H, d, J = 8.2 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.88 (1H, d, J = 3.9 Hz)

ESI-MS (m/e): 534 (M+H).

#### Example 442

##### 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 4-benzyloxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 437, the title compound was obtained by the same process as in Example 438, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 6.57 (1H, brs), 7.23 (1H, brs), 7.46-7.51 (1H, m), 7.57-7.61 (1H, m), 7.64-7.71 (2H, m), 8.06 (1H, d, J = 9.0 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.78 (1H, s), 9.48 (1H, s).

ESI-MS (m/e): 517 (M+H).

#### Example 443

##### 4-(2-cyano-5-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2,4-difluoro-benzonitrile and 4-hydroxy-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 442, the title compound was obtained by same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.20 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.88 (1H, d, J = 10.2 Hz), 6.98 (1H, d, J = 2.0 Hz), 7.05-7.11 (1H, m), 7.39-7.44 (1H, m), 7.68 (1H, dd, J = 3.1, 8.0 Hz), 7.89 (1H, dd, J = 8.8, 6, 1Hz), 8.08-8.12 (1H, m), 8.57-8.60 (1H, m), 8.71 (1H, d, J = 2.3 Hz), 8.77-8.79 (1H, m), 9.46-9.48 (1H, m).

ESI-MS (m/e): 517 (M+H).

#### Example 444

##### 4-(2-cyano-4-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2,5-difluoro benzonitrile, the title compound was obtained by the same process as in Example 443, by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.26 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 6.81 (1H, d, J = 2.3 Hz), 7.22 (1H, dd, J = 4.6, 9.0 Hz), 7.35 (1H, d, J = 2-3 Hz), 7.45 (1H, ddd, J = 8.6, 4.6, 7.4 Hz), 7.63-7.69 (2H, m), 7.72-7.75 (1H, m), 8.09 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 3.1 Hz), 8.72 (1H, d, J = 2.3 Hz), 8.79 (1H, dd, J = 2.0, 3.1 Hz), 9.49 (1H, d, J = 2.0 Hz).

ESI-MS (m/e): 517 (M+H).

**Example 445****4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole**

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 442, the title compound was obtained by same process as in Example 43, by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 6.39 (1H, s), 7.21 (1H, s), 7.42-7.51 (2H, m), 7.55 (1H, dd, J = 8.6, 2.7 Hz), 7.64 (1H, d, J = 7.4 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.75-8.78 (1H, m), 8.82-8.84 (1H, m), 9.54 (1H, brs).

ESI-MS (m/e): 535 (M+H).

**Example 446****4-(6-cyano-pyridin-2-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole**

Using 2-chloro-3-cyanopyridine, the title compound was obtained by the same process as in Example 443, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.25 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 7.14 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 7.4, 5.1 Hz), 7.45 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 9.0, 2.7 Hz), 8.10 (1H, d, J = 9.0 Hz), 8.27-8.33 (2H, m), 8.59 (1H, d, J = 2.7 Hz), 8.70-8.72 (1H, m), 8.76-8.79 (1H, m), 9.41-9.43 (1H, l).

ESI-MS (m/e): 500 (M+H).

**Example 447****4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained as a pale yellow solid by the same process as in Example 438, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 3.23 (3H, s), 6.50 (1H, s), 7.22/(1H, s), 7.45-7.62 (3H, m), 7.62-7.78 (2H, m), 7.95-8.05 (1H, m), 8.08 (1H, d, J = 8.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.49 (1H, s), 8.77 (1H, s).

ESI-MS (m/e): 502 (M+H).

**Example 448****4-(2-fluoro-6-methanesulphonyl-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 2,3-difluoro-methanesulphonyl benzene and 4-hydroxy-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 447, the title compound was



obtained by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.21 (3H, s), 3.46 (3H, s), 6.54 (1H, d, J = 2.0 Hz), 7.27 (1H, d, J = 2.0 Hz), 7.54-7.67 (3H, m), 7.70-7.74 (1H, m), 7.93 (1H, d, J = 7.8 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.11 (1H, ddd, J = 7.8, 8.6, 2.7 Hz), 8.40 (1H, d, J = 7.8 Hz), 8.46 (1H, d, J = 2.7 Hz), 8.86 (1H, d, J = 5.1 Hz).

ESI-MS (m/e): 555 (M+H).

#### Example 449

##### 4-(2-carbamoyl-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole obtained in Example 447, the title compound was obtained by the same process as in Example 43, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.22 (3H, s), 6.53 (1H, d, J = 1.6 Hz), 7.25 (1H, d, J = 1.6 Hz), 7.42-7.53 (2H, m), 7.57 (1H, dd, J = 8.6, 2.7 Hz), 7.61 (1H, d, J = 7.4 Hz), 7.68 (1H, dd, J = 7.6, 14.3 Hz), 8.06 (1H, d, J = 9.0 Hz), 8.10-8.16 (1H, m), 8.41 (1H, d, J = 8.2 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.8.7 (1H, d, J = 4.3 Hz).

ESI-MS (m/e): 520 (M+H).

#### Example 450

##### 4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 6-methanesulphonyl-pyridin-3-ol, the title compound was obtained by the same process as in Example 442, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 3.23 (3H, s), 6.57 (1H, brs), 7.23 (1H, brs), 7.49 (1H, td, J = 8.0, 4.6 Hz), 7.59 (1H, dd, J = 9.0, 3.2 Hz), 7.65-7.71 (2H, m), 8.07 (1H, d, J = 9.0 Hz), 8.50 (1H, d, J = 2.3 Hz), 8.71 (1H, d, J = 2.3 Hz), 8.78 (1H, brs), 9.48 (1H, brs).

ESI-MS (m/e): 503 (M+H).

#### Example 451

##### 4-(pyridin-2-ylsulphonyl)-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-ethanesulphonyl-pyridin-3-ol, the title compound was obtained as pale-brown solid by the same process as in Example 288, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.31 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.03 (1H, d, J = 8.0 Hz),

7.08 (1H, ddd, J = 7.4, 4.7, 1.0 Hz), 7.35 (1H, d, J = 2.2 Hz), 7.38-7.44 (2H, m), 7.52 (1H, td, J = 7.8, 2.0 Hz), 7.64 (1H, d, J = 2.1 Hz), 7.88 (1H, td, J = 7.8, 1.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.38 (1H, d, J = 7.8 Hz), 8.45 (1H, dd, J = 4.9, 1.0 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.64 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 490 (M+H).

#### Example 452

##### 4-(pyridin-2-yl

##### sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 3-(pyridin-2-yl sulphanyl)-5-(6-ethanesulfonyl-pyridin-3-yloxy)-benzene-1,2- diamine obtained in Example 451, the title compound was obtained as yellow solid by the same method as in-Example 68, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.32 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.08-7.19 (2H, m), 7.38 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.6, 2.8 Hz), 7.57 (1H, td, J = 7.8, 1.8 Hz), 7.66 (1H, d, J = 2.2 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.48 (1H, d, J = 4.7 Hz), 8.53 (1H, d, J = 2.7 Hz), 8.63 (1H, t, J = 2.0 Hz), 8.69 (1H, d, J = 2.5 Hz), 9.63 (1H, d, J = 1.4 Hz)

ESI-MS (m/e): 491 (M+H).

#### Example 453

##### 4-(1-methyl-1H-imidazol-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 1-methyl-1H-imidazole-2-thiol, the title compound was obtained as yellow solid by the same process as in Example 452, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.33 (3H, t, J = 7.4 Hz), 3.41 (2H, q, J = 7.4 Hz), 3.94 (3H, s), 6.65-6.69 (1H, m), 6.77 (1H, d, J = 1.4 Hz), 6.87 (1H, d, J = 1.6 Hz), 7.23 (1H, d, J = 2.4 Hz), 7.48 (1H, dd, J = 8.6, 2.8 Hz), 7.72 (1H, d, J = 2.2 Hz), 8.05 (1H, dd, J = 8.6, 0.6 Hz), 8.16 (1H, d, J = 2.6 Hz), 8.54 (1H, dd, J = 2.8, 0.6 Hz), 9.42 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 494 (M+H).

#### Example 454

##### 4-(4-methoxybenzyl-sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using (4-methoxyphenyl) methanethiol, the title compound was obtained as a brown solid by the same process as in Example 452, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.32 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 3.61 and 3.79 (total 3H, each s), 4.05 and 4.40 (total 2H, each s), 6.69 and 6.79 (total 2H, each d, J = 8.6 Hz), 6.88-7.52

(5H, m), 7.98 and 8.01 (total 1H, each d, J = 8.6 Hz), 8.44 and 8.46 (total 1H, each d, J = 2-9 Hz), 8.58-8.65 (1H, m), 8.68 and 8.70 (total 1H, each d, J = 2.5 Hz), 9.58 and 9.74 (d, J = 114 Hz), 10.05 and 10.46 (total 1H, each brs).

ESI-MS (m/e): 534 (M+H).

#### Example 455

4-(6-cyano-pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl -1H-benzimidazole

Using 2-chloro-3-cyanopyridine, the title compound was obtained as a pale yellow solid by the same process as in Example 446, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.32 (3H, t, J = 7.4 Hz), 3.39 (2H, q, J = 7.4 Hz), 7.20 (1H, dd, J = 7.8, 4.9 Hz), 7.41 (1H, d, J = 2.2 Hz), 7.45 (1H, dd, J = 8.8, 2.8 Hz), 7.72 (1H, d, J = 2.2 Hz), 7.93 (1H, dd, J = 7.8, 1.8 Hz), 8.04 (1H, d, J = 8.6 Hz), 8.44 (1H, dd, J = 4.9, 2.0 Hz), 8.54 (1H, d, J = 2.8 Hz), 8.62 (1H, dd, J = 2.5, 1, 5 Hz), 8.70 (1H, d, J = 2.5 Hz), 9.64 (1H, d, J = 1.5 Hz).

ESI-MS (m/e): 516 (M+H).

#### Example 456

4-(2-cyano-pyridin-3-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole

Using 2-cyano-3-fluoropyridine and 4-mercapto-6-(6-ethanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole obtained in Example 455, the title compound was obtained as pale yellow solid by the same process as in Example 438 (Step 2), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.13 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.22 (1H, s), 7.41 (1H, s), 7.64 (2H, dd, J = 8.6, 2.7 Hz), 7.96-8.04 (2H, m), 8.59-8.66 (2H, m), 8.77-8.83 (2H, m), 9.32 (1H, s).

ESI-MS (m/e): 516 (M+H).

#### Example 457

4-(pyridin-2-yl sulphanyl)-5-chloro-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl -1H-benzimidazole

Using pyridine-2-thiol, the title compound was obtained as a pale yellow solid by the same procedures as in Example 117 and Example 290, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.31 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.2 (1H, d, J = 7.5 Hz), 7.05-7.10 (1H, m), 7.31 (1H, dd, J = 8.6, 2.7 Hz), 7.41 (1H, t, J = 6.0 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.75 (1H, s), 7.88 (1H, t, J = 7.8 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.37 (1H, d, J = 8.0 Hz), 8.41 (1H,

d, J = 4.1 Hz), 8.50 (1H, d, J = 2.5 Hz), 8.63 (1H, s).

ESI-MS (m/e): 524,526 (M+H).

#### Examples 458-1, 458-2

4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

and

4-(pyridin-2-yl sulfonyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

To methanol 3 ml solution of 4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole 20 mg obtained in Example 451 were added OXONE 50 mg and water 0.5 ml, and the reaction liquor was stirred at room temperature for three hours. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was diluted with ethyl acetate and was washed with water and thereafter, was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid]. Saturated aqueous sodium bicarbonate was added to the obtained fraction and thereafter, it was extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

4-(pyridin-2-yl sulphanyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.33 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.35 (1H, dd, J = 8.8, 2.7 Hz), 7.37-7.45 (2H, m), 7.55 (1H, d, J = 2.1 Hz), 7.61 (1H, d, J = 2.1 Hz), 7.89 (1H, t, J = 7.8 Hz), 7.96 (1H, t, J = 7.8 Hz), 8.02 (1H, d, J = 8.6 Hz), 8.15 (1H, d, J = 8.2 Hz), 8.37 (1H, d, J = 7.8 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.65 (1H, d, J = 3.7 Hz), 8.76 (1H, d, J = 4.5 Hz).

ESI-MS(m/e): 506 (M+H).

4-(pyridin-2-yl sulfonyl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.33 (3H, t, J = 7.4 Hz), 3.40 (2H, q, J = 7.4 Hz), 7.37 (1H, dd, J = 8.6, 2.8 Hz), 7.44-7.49 (1H, m), 7.55 (1H, dd, J = 7.4, 4.5 Hz), 7.70 (1H, d, J = 1, 8 Hz), 7.80 (1H, d, J = 2.2 Hz), 7.88-7.94 (1H, m), 7.96-8.02 (1H, m), 8.04 (1H, d, J = 8.6 Hz), 8.26 (1H, d, J = 7.4 Hz), 8.40 (1H, d, J = 8.0 Hz), 8.49 (1H, d, J = 2.7 Hz), 8.73 (1H, d, J = 4.7 Hz), 8.77 (1H, d, J = 4.9 Hz).

ESI-MS (m/e): 522 (M+H).

**Example 459**6-(1-acetyl pyrrolidin-2-yl)-5-((2'-fluoro biphenyl-4-yl) oxy)-2-pyridin-2-yl-1H- benzimidazole

Using 2'-fluoro biphenyl-4-ol, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.00-2.60 (7H, m), 3.40-4.00 (2H, m), 5.20-5.65 (1H, m), 7.00-7.70 (11H, m), 7.80-8.00 (1H, m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, 1).

ESI-MS (m/e): 493 (M+H).

**Example 460**6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H- benzimidazole •  
monotrifluoroacetic acid salt**Step 1**Synthesis of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy)  
methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde

To N-methyl-2-pyridine diol 1 ml solution of 1-(2-(6-hydroxy-2-pyridin-2-yl-3-(2-trimethylsilyl-ethoxymethyl)-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone 100 mg obtained in Example 121 (Step 11) were added successively cesium carbonate 143 mg, p-fluoro benzaldehyde 0.048 ml, and the reaction liquor was heated with stirring at 80°C for three hours. The reaction liquor was cooled to room temperature, and saturated ammonium chloride aqueous solution was added, and the mixture was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution. After drying, the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: chloroform-methanol = 100/1) and the title compound was obtained as orange oily substance.

**Step 2**Synthesis of 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H-  
benzimidazole

To chloroform 0.2 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde 22 mg, bis (2-methoxyethyl) amino sulphur trifluoride 0.036 ml was added, and the reaction liquor was heated with stirring at 80°C for eight hours. The solvent was eliminated by distillation under reduced pressure, then the residue was purified by preparative thin layer chromatography (Kieselgel TM60F254, Art5744 (Merck Corporation), chloroform/methanol = 9/1), and the title compound was obtained as yellow solid.

## Step 3

Production of 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole • monotrifluoroacetic acid salt

Trifluoroacetic acid 0.5 ml was added to 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(difluoromethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole 12 mg, and the reaction liquor was stirred at room temperature for one hour. Trifluoroacetic acid was eliminated by distillation under reduced pressure, and thereafter the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as red oily substance.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 0.78-0.95 (4H, m), 1.91-2.15 (2H, m), 2.69 (3H, s), 5.38-5.43 (1H, m), 7.21-7.34 (4H, m), 7.52-7.63 (6H, m), 8.27-8.29 (1H, m).

ESI-MS (m/e): 449 (M+H).

## Example 461

1-(2-(6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (3-chloro-4-methanesulphonyl) phenol, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.85-2.40 (4H, m), 2.90-3.27 (5H, m), 3.65-3.90 (2H, m), 5.15-5.43 (1H, m), 6.90-7.45 (5H, m), 7.84-8.15 (2H, m), 8.35-8.42 (1H, m), 8.60-8.68 (1H, m).

ESI-MS (m/e): 511 (M+H).

## Example 462

2-(6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methanesulphonyl) phenoxy)-1H-benzimidazol-2-yl) (1,3) thiazolo (5,4-b) pyridine • monotrifluoroacetic acid salt

Using 2-(4,5-diamino-2-(4-methanesulphonyl-phenoxy)-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained in Example 306 (Step 3) and (1,3) thiazolo (5,4-b) pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 306 (Step 4) and (Step 5), by a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.60-2.40 (7H, m), 3.00-3.80 (5H, m), 5.00-5.60 (1H, m), 7.20-7.40 (2H, m), 7.25-7.80 (3H, m), 7.90-8.10 (2H, m), 8.40-8.80 (2H, m).

ESI-MS (m/e): 534 (M+H).

## Example 463

5-(1-acetyl pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-(5-(trifluoromethyl)

pyridin-2-yl)-1H-benzimidazole

Using 5-(trifluoromethyl) pyridine-2-carboxylic acid, the title compound was obtained as a white solid by the same process as in Example 462, by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 0.89 (1H, m), 1.22 (2H, m), 1.88-2.11 (3H, m), 2.27 (1H, m), 3.08 (3H, m), 3.63-3.76 (1H, m), 3.84 (1H, s), 5.38 (1H, dd, J = 25.8, 8.6 Hz), 7.11-7.20 (2H, m), 7.39 (1H, m), 7.54 (1H, m), 7.93 (2H, m), 8.11 (1H, m), 8.51 (1H, m), 8.93 (1H, m), 10.58-10.88 (1H, m).

ESI-MS (m/e): 545 (M+H).

**Example 464**6-(1-acetyl pyrrolidin-2-yl)-2-(5-(difluoromethyl) pyridin-2-yl)-5-(4-methanesulphonyl phenoxy)-1H-benzimidazole • monotrifluoroacetic acid salt

Using 5-(difluoromethyl) pyridine-2-carboxylic acid, the title compound was obtained as a yellow oily substance by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 0.92 (1H, m), 1.32 (2H, m), 1.89 (1H, m), 1.97-2.08 (2H, m), 2.13-2.14 (1H, m), 2.69 (3H, s), 3.16-3.17 (3H, s), 5.35 (1H, m), 7.30-7.32 (1H, m), 7.41-7.58 (1H, m), 7.60-7.62 (1H, m), 8.00-8.02 (3H, m), 8.04-8.22 (2H, m), 9.04 (1H, m).

ESI-MS (m/e): 527 (M+H).

**Example 465**6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl- 1H-benzimidazole • monotrifluoroacetic acid salt

To methanol 0.5 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol -5-yl) oxy) benzaldehyde 50 mg obtained in Example 460 (Step 1) was added hydroxylation boron sodium 7 mg under ice cooling, and the reaction liquor was stirred for one hour. Saturated ammonium chloride aqueous solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To dimethylformamide 1 ml solution of the obtained crude product, sodium hydride 10 mg and methyl iodide 0.030 ml were added successively and stirred at room temperature for 30 minutes. Saturated ammonium chloride aqueous solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Trifluoroacetic acid 0.5 ml was added to the obtained crude product, and the reaction liquor was

stirred at room temperature for two hours. Trifluoroacetic acid was eliminated by distillation under reduced pressure, and thereafter the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.93 (1H, m), 2.07-2.11 (3H, m), 2.18 (2H, m), 2.45 (1H, m), 3.43 (3H, d, J = 3-Hz), 3.75-3.95 (2H, m), 4.50 (d, 2H, J = 4-3 Hz), 5.49-5.56 (1H, m), 7.16 (3H, m), 7.44-7.49 (2H, m), 7.57 (1H, m), 7.70-7.73 (1H, m), 8.15 (1H, m), 8.27-8.30 (1H, m), 8.89 (1H, m).

ESI-MS (m/e): 443 (M+H).

#### Example 466

1-(4-(6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl)-1H-benzimidazol-5-yl) oxy) phenyl) ethanol • monotrifluoroacetic acid salt

To tetrahydrofuran 1.3 ml solution of 4-(6-(1-(acetyl pyrrolidin-2-yl)-2-pyridin-2-yl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-benzimidazol-5-yl) oxy) benzaldehyde 70 mg obtained in Example 460 (Step 1) was added methyllithium (1.0M diethyl ether solution) 0.4 ml at -78°C, and the reaction liquor was stirred at 78°C for 30 minutes. Saturated ammonium chloride solution was added to the reaction liquor and extraction was carried out with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Trifluoroacetic acid 0.5 ml was added to the obtained crude product and stirred at room temperature for 90 minutes, and thereafter, trifluoroacetic acid was eliminated by distillation under reduced pressure, and the residue was purified using reverse phase medium pressure liquid chromatography [ODS-AS-360-CC (made by YMC) mobile phase: water-acetonitrile-0.1% trifluoroacetic acid], and solvent of the obtained fraction was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow oily substance.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 0.90-0.96 (1H, m), 1.31 (4H, m), 1.25-1.90 (3H, m), 2.42 (1H, m), 2.68 (3H, s), 3.89-3.91 (1H, m), 5.50 (1H, m), 7.02-7.33 (4H, m), 7.42-7.52 (2H, m), 7.59-7.67 (1H, m), 8.10-8.14 (1H, m), 8.22-8.26 (1H, m), 8.80-8.87 (1H, m).

ESI-MS (m/e): 443 (M+H).

#### Example 467

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(3-methyl-[1,2,4]-oxadiazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 5-(4-iodophenyl)-3-methyl-[1,2,4]-oxadiazole, the title compound was obtained as dark brown oily substance by the same process as in Example 122, a process based on this or a



combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.39-2.49 (10H, m), 3.42-3.88 (2H, m), 5.14-5.4 (1H, m), 6.70-8.69 (10H, m).

ESI-MS (m/e): 481 (M+H).

#### Example 468

(1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A

##### Step 1

Synthesis of 3-((t-butyl (dimethyl) silyl) oxy) dihydrofuran-2 (3H)-one

In 3-hydroxy dihydrofuran-2 (3H)-one 9.0 g dissolved in dimethylformamide 180 ml were added successively imidazole 9.0 g, t-butyl dimethylsilyl chloride 15.9 g, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with ethyl acetate and was washed using water, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as colourless oily supplies.

##### Step 2

Synthesis of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-4-hydroxy butanoyl)-3-fluorophenyl) pyridine-2-carboxamide

In N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.1 g dissolved in tetrahydrofuran 100 ml, n-butyllithium (2.66M hexane solution) 3.1 ml was added dropwise at -78°C, and the reaction liquor was stirred at the same temperature for 15 minutes. 3-((t-butyl (dimethyl) silyl) oxy) dihydrofuran-2 (3H)-one 1.21 g was added to the reaction liquor, and the reaction liquor was stirred at the same temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and it was warmed to room temperature, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was dried with anhydrous sodium sulphate, and thereafter the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1), and the title compound was obtained as a colourless oily substance.

##### Step 3

Synthesis of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-1,4-dihydroxy butyl)-3-fluorophenyl) pyridine-2-carboxamide

To methanol 20 ml solution of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-4-hydroxy butanoyl)-3-fluorophenyl) pyridine-2-carboxamide 860 mg was added sodium borohydride 114

mg under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1) and the title compound was obtained as a white solid.

#### Step 4

##### Synthesis of N-(4-(3-((t-butyl (dimethyl) silyl) oxy) pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide

Triethylamine 155 mg and methanesulfonyl chloride 130 mg were added under ice cooling successively to chloroform 8 ml solution of N-(4-(2-((t-butyl (dimethyl) silyl) oxy)-1,4-dihydroxybutyl)-3-fluorophenyl) pyridine-2-carboxamide 165 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 5 ml solution of the obtained residue was added sodium azide 25 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and sodium borohydride 50 mg and copper sulfate • pentahydrate 5 mg were added successively to methanol 10 ml solution of the obtained residue, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, saturated aqueous sodium bicarbonate was added and was extracted with chloroform, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 50/1) and the title compound was obtained as a colourless oily substance.

#### Step 5

##### Synthesis of 1-acetyl-2-(2-fluoro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate

To methanol 1 ml solution of N-(4-(3-((t-butyl (dimethyl) silyl) oxy) pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide 59 mg was added 4 N hydrochloric acid-dioxane 2 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and triethylamine 100 mg, acetic anhydride 90 mg, N,N-4-dimethylaminopyridine 5 mg were added successively to chloroform 5 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure and the obtained

residue was purified using silica gel chromatography (eluent: chloroform / methanol = 200/1), and obtained the title compound as a colourless oily substance.

#### Step 6

Synthesis of 1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate diastereomer A and diastereomer B

Fuming nitric acid 1 ml was added to N-(4-(3-((t-butyl (dimethyl) silyl) oxy)-pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide 57 mg, and the reaction liquor was stirred at room temperature for 40 minutes. The reaction liquor was discharged into mixed solution of ice-saturated aqueous sodium bicarbonate and was extracted with chloroform, then dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Corporation), chloroform/methanol = 20/1), and respectively obtained diastereomer A and diastereomer B of the title compound as a yellow oily substance.

#### Step 7

Production of 1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A

Using 4-(methanesulphonyl) phenol and (1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl acetate diastereomer A, the title compound was obtained as a white solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.86-2.42 (8H, m), 3.04-3.10 (3H, m), 3.72-4.02 (2H, m), 5.06-5.38 (2H, m), 7.08-7.70 (5H, m), 7.83-7.97 (3H, m), 8.34-8.42 (1H, m), 8.61-8.68 (1H, m), 10.54-10.65 (1H, m).

ESI-MS (m/e): 535 (M+H).

#### Example 469

1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-ol diastereomer A

To methanol 2 ml solution of (1-acetyl-2-(5-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-yl acetate diastereomer A 14 mg obtained in Example 468 was added potassium carbonate 5 mg, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Corporation), chloroform/methanol = 15/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.82-2.47 (5H, m), 3.05&3.08 (3H, s), 3.70-3.97 (2H, m), 4.29-4.45 (1H, m), 5.00-5.32 (1H, m), 7.00-7.67 (5H, m), 7.81-7.96 (2H, m), 8.00-8.42 (1H, m), 8.60-8.69 (1H, m), 10.62-10.85 (1H, m).

ESI-MS (m/e): 493 (M+H).

#### Example 470

6-(1-acetyl-4,5-dihydro-1H-pyrrole-2-yl)-5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To chloroform 1 ml solution of 1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-3-ol diastereomer A 2 mg obtained in Example 469 was added bis (2-methoxyethyl) amino sulphur trifluoride 2 mg, and the reaction liquor was stirred at room temperature for 15 minutes. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Corporation), chloroform/methanol = 15/1), and obtained the title compound as a colourless oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-4.43 (10H, m), 7.03-7.80 (6H, m), 7.82-7.95 (3H, m), 8.32-8.46 (1H, m), 8.60-8.71 (1H, m), 10.38-10.60 (1H, m).

ESI-MS (m/e): 475 (M+H).

#### Example 471

1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)pyrrolidin-3-yl acetate diastereomer B

Using (1-acetyl-2-(2-fluoro-5-nitro-4-((pyridin-2-ylcarbonyl) amino) phenyl) pyrrolidin-3-yl) diastereomer B obtained in Example 468 (Step 6), the title compound was obtained by the same process as in Example 468 (Step 7), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.72-2.30 (8H, m), 3.02-3.08 (3H, m), 3.64-3.99 (2H, m), 5.26-5.47 (1H, m), 5.58-5.72 (1H, m), 7.09-7.73 (5H, m), 7.82-7.94 (3H, m), 8.33-8.43 (1H, m), 8.60-8.70 (1H, m), 10.47-10.68 (1H, m).

ESI-MS (m/e): 535 (M+H).

#### Example 472

1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)pyrrolidin-3-ol diastereomer B

Using (1-acetyl-2-(5-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)pyrrolidin-3-yl acetate diastereomer B obtained in Example 471, the title compound was obtained by the same process as in Example 469, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.78-2.25 (5H, m), 3.03-3.10 (3H, m), 3.60-4.00 (2H, m), 4.50-4.68 (1H, m), 5.27-5.45 (1H, m), 7.03-7.73 (5H, m), 7.81-7.96 (3H, m), 8.32-8.45 (1H, m), 8.60-8.69 (1H, m), 10.51-10.82 (1H, m).

ESI-MS (m/e): 493 (M+H).

#### Example 473

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) piperidin-2-one

Using 1-(4-hydroxyphenyl) piperidin-2-one, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.74-2.62 (13H, m), 3.52-3.87 (4H, m), 5.18-5.36 (1H, m), 6.71-7.64 (7H, m), 7.76-7.90 (1H, m), 8.26-8.41 (1H, m), 8.56-8.68 (1H, m), 10.98-11.33 (1H, m).

ESI-MS (m/e): 496 (M+H).

#### Example 474

6-(1-acetyl pyrrolidin-2-yl)-5-((6-phenyl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-phenyl pyridin-3-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.40-2.50 (7H, m), 3.40-4.00 (2H, m), 5.20-5.60 (1H, m), 6.90-8.00 (11H, m), 8.20-8.45 (1H, m), 8.50-8.70 (2H, m), 10.60-10.90 (1H, m).

ESI-MS (m/e): 476 (M+H).

#### Example 475

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-fluorophenyl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(2-fluorophenyl) pyridin-3-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.60-2.50 (7H, m), 3.45-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.05 (10H, m), 8.30-8.45 (1H, m), 8.50-8.70 (2H, m), 10.80-11.20 (1H, m).

ESI-MS (m/e): 494 (M+H).

#### Example 476

1-(2-(6-(3-fluoro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using (3-fluoro-4-methanesulphonyl) phenol, the title compound was obtained as yellow solid by

the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.87-2.38 (4H, m), 2.85-3.27 (5H, m), 3.60-3.95 (2H, m), 5.20-5.41 (1H, m), 6.83-7.00 (1H, m), 7.28-7.40 (4H, m), 7.81-7.98 (2H, m), 8.35-8.42 (1H, m), 8.60-8.68 (1H, m).

ESI-MS (m/e): 495 (M+H).

#### Example 477

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyrrolidin-2-one

Using 1-(4-hydroxyphenyl) pyrrolidin-2-one, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.40 (6H, m), 2.62 (2H, m), 3.55-3.95 (4H+1/2H, m), 5.28 (1/2H, m), 6.90-7.10 (3H, m), 7.35 (1H+1/2H, m), 7.45-7.65 (2H+1/2H, m), 7.85 (1H, m), 8.34 (1H, m), 8.61 (1H, m), 10.4-10.8 (1H, br).

ESI-MS (m/e): 482 (M+H).

#### Example 478

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) pyridine-2 (1H)-one

Using 1-(4-hydroxyphenyl) pyridine-2 (1H)-one, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.72-2.42 (7H, m), 3.48-3.86 (2H, m), 5.15-5.52 (1H, m), 6.19-6.32 (1H, m), 6.61-6.73 (1H, m), 6.80-7.66 (9H, m), 7.77-7.89 (1H, m), 8.32-8.41 (1H, m), 8.52-8.65 (1H, m), 11.07-11.48 (1H, m).

ESI-MS (m/e): 492 (M+H).

#### Example 479

5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridine-2-yl-1H-benzimidazol-5-yl) oxy)-2,2'-bipyridine • monotrifluoroacetic acid salt

Using 2,2'-bipyridine-5-ol, the title compound was obtained as yellow solid by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.80-2.80 (7H, m), 3.160-4.05 (2H, m), 5.20-5.60 (1H, m), 7.50-7.90 (4H, m), 8.00-8.15 (1H, m), 8.15-8.25 (1H, m), 8.30-8.40 (1H, m), 8.45-8.60 (1H, m), 8.60-9.00 (5H, m).

ESI-MS (m/e): 477 (M+H).

**Example 480**

N-(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-methane sulfonamide

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) and N-t-butoxycarbonyl-glycine, the title compound was obtained by the same procedures as in Example 171 and Example 178, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.93-2.14 (3H, m), 2.06-2.27 (1H, m), 2.86 and 2.95 (total 3H, each s), 3.13 (3H, s), 3.43-4.08 (4H, m), 5.20-5.38 (1H, m), 7.20-7.60 (5H, m), 7.93-8.02 (3H, m), 8.23-8.30 (1H, m), 8.74 (1H, brs).

ESI-MS (m/e): 570 (M+H).

**Example 481**

(2-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-oxo-ethyl)-ethyl carbamate ester

Using 5-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-6-pyrrolidin-2-yl-1H-benzimidazole obtained in Example 162 (Step 7) and N-t-butoxycarbonyl-glycine, the title compound was obtained by the same procedures as in Example 171 and Example 181, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.18 and 1.23 (total 3H, each t, J = each 7.1 Hz), 1.93-2.14 (3H, m), 2.22-2.44 (1H, m), 3.12 and 3.13 (total 3H, each s), 3.30-4.13 (6H, m), 5.24-5.33 (1H, m), 7.20-7.60 (5H, m), 7.93-8.01 (3H, m), 8.28 (1H, t, J = 8.2 Hz), 8.73 (1H, brs).

ESI-MS (m/e): 564 (M+H).

**Example 482**

6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer

A

**Step 1**

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2- carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide 100 mg obtained by Example 338 (Step 4) was optically-resolved by a column for optical resolution (CHIRALPAK OD 2 cm $\phi$  x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 60/40/0.1, flow rate: 10 ml/min), and enantiomer A (retention time: 17.8 min), enantiomer B (retention time: 21.0 min) were respectively obtained as pale yellow solid.

**Step 2**Production of 6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Using N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer A obtained in Example 482 (Step 1) and 4-bromo(sic)phenol, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR, (CDCl<sub>3</sub>) δ : 1.56-2.41 (7H, m), 3.42-3.90 (2H, m), 5.16-5.51 (1H, m), 6.78-7.66 (7H, m), 7.80-7.93 (1H, m), 8.32-8.44 (1H, m), 8.54-8.67 (1H, m), 11.14-11.65 (1H, m).

ESI-MS (m/e): 479 (M+H).

**Example 483**6-(1-acetyl pyrrolidin-2-yl)-5-(4 bromo phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

Using N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 482 (Step 1) and 4-bromo(sic)phenol, the title compound was obtained as an oily substance by the same process as in Example 338 (Step 5), by a process based on this or a combination of these with a normal procedure.

ESI-MS (m/e): 479 (M+H).

**Examples 484**6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.51-2.43 (7H, m), 2.59-2.74 (3H, m), 3.50-3.93 (2H, m), 5.17-5.46 (1H, m), 7.00-7.72 (4H, m), 7.82-8.13 (2H, m), 8.34-8.44 (1H, m), 8.57-8.69 (2H, m), 10.75-11.14 (1H, m).

ESI-MS (m/e): 482 (M+H).

**Example 485**5-(1-acetyl-3-methylpyrrolidin-2-yl)-6-(4-(methylsulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole**Step 1**Synthesis of N-(3-fluoro-4-[2-(2-hydroxyethyl) acryloyl] phenyl) pyridine-2-carboxamide

To N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.0 g dissolved in tetrahydrofuran 20 ml solution, 60 % sodium hydride 136 mg was added under ice cooling, and the reaction liquor was



stirred at the same temperature for 15 minutes. The reaction liquor was cooled to  $-78^{\circ}\text{C}$ , and thereafter, n-butyllithium (2.66M hexane solution) 1.53 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 30 minutes. 3-methylene dihydro-furan-2(3H)-one 0.36 ml was added to the reaction liquor at the same temperature, and the reaction liquor was stirred at the same temperature for two hours, and thereafter, it was warmed to  $0^{\circ}\text{C}$ , and it was stirred for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and the mixture was extracted with ethyl acetate, and the organic layer was washed using saturated aqueous sodium chloride solution, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained as a colourless oily substance.

### Step 2

#### Synthesis of N-(4-[1,4-dihydroxy-2-methyl butyl]-3-fluorophenyl) pyridine-2-carboxamide

To methanol 8 ml solution of N-(3-fluoro-4-(2-[2-hydroxyethyl) acryloyl) phenyl) pyridine-2-carboxamide 320 mg, sodium borohydride 150 mg was added, and the reaction liquor was stirred at room temperature for one hour. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform / methanol = 100/1) and the title compound was obtained as a colourless oily substance.

### Step 3

#### Synthesis of N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide

To chloroform 5 ml solution of N-(4-(1,4-dihydroxy-2-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide 100 mg were added successively triethylamine 0.18 ml, methanesulfonyl chloride 0.07 ml, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 4 ml solution of the obtained residue was added sodium azide 23 mg, and the reaction liquor was stirred at  $40^{\circ}\text{C}$  for two hours. The reaction liquor was cooled to room temperature, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and, to methanol 5 ml solution of the obtained residue were added successively sodium borohydride 50 mg, copper sulfate • pentahydrate 5 mg, and the reaction liquor was stirred at  $40^{\circ}\text{C}$  for 15 minutes. The reaction liquor was cooled to room temperature, and thereafter, saturated aqueous sodium bicarbonate was added, extraction was carried out with chloroform and dried with anhydrous

sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 4 ml solution of the obtained residue were added successively triethylamine 0.08 ml, acetic anhydride 0.07 ml, N,N-4-dimethylaminopyridine 5 mg, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform / methanol = 100/1) and the title compound was obtained as a colourless oily substance.

#### Step 4

##### Synthesis of N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)pyridine-2-carboxamide

Fuming nitric acid 1 ml was added to N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-3-fluorophenyl)pyridine-2-carboxamide 70 mg, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was discharged into ice-saturated aqueous sodium bicarbonate mixed solution, extracted with chloroform, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined using preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and thereby obtained the title compound as yellow solid.

#### Step 5

##### Production of 5-(1-acetyl-3-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl)phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using N-(4-(1-acetyl-3-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)pyridine-2-carboxamide and 4-(methanesulphonyl)phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.81-2.73 (9H, m), 3.03-3.11 (3H, m), 3.36-3.99 (2H, m), 4.65-5.43 (1H, m), 7.00-7.75 (5H, m), 7.81-7.79 (3H, m), 8.32-8.45 (1H, m), 8.60-8.68 (1H, m), 10.51-10.82 (1H, br).

ESI-MS (m/e): 491 (M+H).

#### Example 486

##### 6-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)-3,4-dihydro-naphthalene-1(2H)-one

Using 6-hydroxy-3,4-dihydro-naphthalene-1(2H)-one, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.00-3.00 (13H, m), 3.40-3.95 (2H, m), 5.00-5.50 (1H, m), 6.60-7.80 (5H, m), 7.80-8.20 (2H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m), 10.80-11.20 (1H, m).

ESI-MS (m/e): 467 (M+H).

#### Example 487

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1H-imidazol-1-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1H-imidazol-1-yl) phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.00-2.50 (7H, m), 3.50-4.50 (2H, m), 5.20-6.00 (1H, m), 6.80-8.80 (13H, 13).

ESI-MS (m/e): 465 (M+H).

#### Example 488

6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-1-methyl-[1,2,3,4]-tetrahydronaphthalene-1-ol

To tetrahydrofuran 0.5 ml solution of 6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1 (2H)-one 7 mg obtained in Example 486 was added methylmagnesium bromide (5.0M tetrahydrofuran solution) 0.050 ml under ice cooling, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with chloroform, washed with saturated ammonium chloride aqueous solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound was obtained as a colourless oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.10-2.80 (16H, m), 3.50-4.00 (2H, m), 5.10-5.50 (1H, m), 6.60-7.90 (7H, m), 8.30-8.50 (1H, m), 8.50-70 (1H, m).

ESI-MS (m/e): 465 (M+H).

#### Example 489

6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-[1,2,3,4]-tetrahydronaphthalene-1-ol

To tetrahydrofuran 0.5 ml solution of 6-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-3,4-dihydro-naphthalene-1 (2H)-one 7 mg obtained in Example 486 was added sodium borohydride 5 mg under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with chloroform, washed with saturated ammonium chloride aqueous solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced

pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a colourless oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.00-2.50 (14H, m), 4.00-6.00 (3H, m), 6.80-8.50 (9H, m).

ESI-MS (m/e): 469 (M+H).

#### Example 490

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer A

##### Step 1

Synthesis of ethyl (2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoate

Tetrahydrofuran 40 ml solution of (diethoxy phosphoryl) (fluoro) ethyl acetate 2.0 g was cooled to -78°C, and thereafter, n-butyllithium (2.66M hexane solution) 3.4 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 15 minutes. To the reaction liquor was added ((t-butyl (dimethyl) silyl) oxy) acetaldehyde 2.1 ml, and the reaction liquor was stirred at the same temperature for two hours. Saturated aqueous sodium bicarbonate was added to the reaction solution at the same temperature, and it was warmed to room temperature, and thereafter, extraction was carried out with ethyl acetate. It was dried using anhydrous sodium sulfate, and next the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 50/1) and the title compound was obtained as a colourless oily substance.

##### Step 2

Synthesis of N-(4-((2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoyl)-3-fluorophenyl) pyridine-2-carboxamide

To N-(4-bromo-3-fluorophenyl) pyridine-2-carboxamide 1.0 g dissolved in tetrahydrofuran 40 ml solution, 60 % sodium hydride 136 mg was added under ice cooling, and the reaction liquor was stirred at the same temperature for 20 minutes. The reaction liquor was cooled to -78°C, and thereafter, n-butyllithium (2.66M hexane solution) 1.53 ml was added dropwise, and the reaction liquor was stirred at the same temperature for 20 minutes. Ethyl (2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluorobut-2-enoate 1.07 g was added to the reaction liquor at the same temperature, and the reaction liquor was stirred at the same temperature for four hours. Saturated aqueous sodium bicarbonate was added to the reaction liquor at the same temperature, and it was warmed to room temperature, and thereafter, it was extracted with ethyl acetate, and the organic layer was washed using saturated aqueous sodium chloride solution, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: hexane / ethyl acetate = 3/1) and the title

compound was obtained as a colourless oily substance.

### Step 3

#### N-(4-(4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro-1-hydroxy butyl)-3-fluorophenyl) pyridine-2-carboxamide

To methanol 20 ml solution of N-(4-((2Z)-4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro but-2-enoyl)-3-fluorophenyl) pyridine-2-carboxamide 300 mg was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for four hours. The catalyst was filtered, and the solvent was eliminated by distillation under reduced pressure, and, to methanol 4 ml solution of the obtained residue was added sodium borohydride 50 mg, and the reaction liquor was stirred at room temperature for one hour.

Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel chromatography (eluent: chloroform/methanol = 100/1) and the title compound was obtained as a colourless oily substance.

### Step 4

#### Synthesis of N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereoisomer A and diastereomer B

To chloroform 5 ml solution of N-(4-(4-((t-butyl (dimethyl) silyl) oxy)-2-fluoro-1-hydroxybutyl)-3-fluorophenyl) pyridine-2-carboxamide 100 mg were added successively triethylamine 46 mg, methanesulfonyl chloride 39 mg, and the reaction liquor was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate was added to the reaction liquor, and extraction was carried out with chloroform and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to dimethylformamide 4 ml solution of the obtained residue was added sodium azide 22 mg, and the reaction liquor was stirred at 40°C for two hours. The reaction liquor was cooled, and thereafter, water was added, and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and tetrabutyl ammonium fluoride (1.0M tetrahydrofuran solution) 0.3 ml was added to tetrahydrofuran 4 ml solution of the obtained residue, and the reaction liquor was stirred at room temperature for one hour. To the reaction liquor, water was added and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 5 ml solution of the obtained residue were added successively triethylamine 46 mg, methanesulfonyl chloride 39 mg,

and the reaction liquor was stirred at room temperature for 30 minutes. To the reaction liquor, saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate, and drying was carried out with anhydrous sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and copper sulfate • pentahydrate 10 mg, sodium borohydride 50 mg were added successively to methanol 4 ml solution of the obtained residue, and the reaction liquor was stirred at 40°C for one hour. The reaction liquor was cooled, and thereafter, saturated aqueous sodium bicarbonate was added, and extraction was carried out with chloroform and the chloroform layer was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and, to chloroform 4 ml solution of the obtained residue were added successively triethylamine 46 mg, acetic anhydride 35 mg, N,N-4-dimethylaminopyridine 5 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using preparative thin layer chromatography (chloroform/methanol = 30/1) and the title compounds diastereomer A and diastereomer B were respectively obtained as a colourless oily substance.

#### Step 5

##### Production of 5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer A

Fuming nitric acid 0.5 ml was added to N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereomer A 18 mg, and the reaction liquor was stirred at room temperature for ten minutes. The reaction liquor was discharged into ice-saturated aqueous sodium bicarbonate mixed solution, extracted with chloroform, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. Using the obtained composition(sic) product and 4-(methanesulphonyl) phenol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.85-2.40 (5H, m), 3.06 and 3.09 (3H, s), 3.79-4.08 (2H, m), 4.96-5.62 (2H, m), 7.05-7.70 (5H, m), 7.83-7.99 (3H, m), 8.34-8.43 (1H, m), 8.61-8.69 (1H, m), 10.58-10.84 (1H, m).

ESI-MS (m/e): 495 (M+H).

#### Example 491

##### 6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-(4-(2-thienyl) phenoxy)-1H-benzimidazole

Using 4-(2-thienyl) phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.05-2.45 (7H, m), 3.40-4.00 (2H, m), 5.10-5.60 (1H, m), 6.80-8.00 (11H, m), 8.30-8.50 (1H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 481 (M+H).

#### Example 492

2-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1H-indole-1,3 (2H)-dione

Using 2-(4-hydroxyphenyl)-1H-indole-1,3 (2H) dione, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.05-2.40 (7H, m), 3.40-4.05 (2H, m), 5.05-5.60 (1H, m), 6.80-8.20 (12H, m), 8.30-8.70 (2H, m).

ESI-MS (m/e): 544 (M+H).

#### Example 493

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer B

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-3-fluorophenyl) pyridine-2-carboxamide diastereomer B obtained by Example 490 (Step 4), the title compound was obtained as pale yellow solid in accordance with Example 490 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.45 (5H, m), 3.05 and 3.08 (3H, s), 3.61-4.31 (2H, m), 5.08-5.54 (2H, m), 7.03-7.80 (5H, m), 7.81-7.97 (3H, m), 8.33-8.43 (1H, m), 8.60-8.68 (1H, m), 10.52-10.75 (1H, 1).

ESI-MS (m/e): 495 (M+H).

#### Example 494

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-1H-tetrazol-1-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(5-methyl-1H-tetrazol-1-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ: 1.91 and 2.15 (total 3H, each s), 1.97-2.20 (3H, m), 2.22-2.58 (1H, m), 2.63 and 2.64 (total 3H, each s), 3.62-4.00 (2H, m), 5.34-5.42 (1H, m), 7.22-7.68 (7H, m), 7.94-8.05 (1H, m), 8.30 (1H, t, J = 7.8 Hz), 8.76 (1H, brs).

ESI-MS (m/e): 481 (M+H).

#### Example 495

Ethyl 5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)  
pyridine-2-carboxylate

Using ethyl 5-hydroxypyridine-2-carboxylate, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.30-1.50 (3H, m), 1.50-2.50 (7H, m), 3.50-3.90 (2H, m), 4.35-4.60 (2H, m), 5.10-5.45 (1H, m), 6.90-7.70 (4H, m), 7.80-7.95 (1H, m), 8.00-8.20 (1H, m), 8.30-8.80 (3H, m), 10.60-11.20 (1H, m).

ESI-MS (m/e): 472 (M+H).

**Example 496**

6-(1-acetyl pyrrolidin-2-yl)-5-(4-pyrazin-2-yl phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-pyrazin-2-yl phenol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.80-2.40 (7H, m), 3.60-3.90 (2H, m), 5.20-5.60 (1H, m), 6.80-8.05 (8H, m), 8.30-8.80 (4H, m), 8.90-9.10 (1H, m), 10.40-10.80 (1H, m).

ESI-MS (m/e): 477 (M+H).

**Example 497**

6-(1-acetyl pyrrolidin-2-yl)-5-(1H-indol-5-yloxy)-2-pyridin-2-yl-1H-benzimidazole

Using 1H-indole-5-ol, title-compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.40 (7H, m), 3.60-4.00 (2H, m), 5.20-5.60 (1H, m), 6.40-6.60 (1H, m), 6.80-8.00 (7H, m), 8.20-8.50 (2H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 438 (M+H).

**Example 498**

(2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)  
pyrrolidin-1-yl)-2-oxoethyl) methylamine

**Step 1**

Synthesis of (3-fluoro-4-pyrrolidin-2-yl phenyl) amine dihydrochloride

To mixed solution of methanol 50 ml and ethyl acetate 50 ml of 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 19 g obtained in Example 338 (Step 2) was added 4 N hydrochloric acid-dioxane solution 100 ml under ice cooling, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a white solid.



**Step 2****Synthesis of 2,2,2-trifluoro-N-(3-fluoro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide**

To (3-fluoro-4-pyrrolidin-2-yl phenyl) amine dihydrochloride 20 g suspended in chloroform 200 ml were added successively pyridine 39 ml and trifluoroacetic anhydride 24 ml under ice cooling, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as brown oily substance.

**Step 3****Synthesis of 2,2,2-trifluoro-N-(5-fluoro-2-nitro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide**

Fuming nitric acid 100 ml was added under ice cooling to 2,2,2-trifluoro-N-(3-fluoro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide 28 g, and the reaction liquor was stirred at room temperature for one hour. Iced water was added to the reaction liquor and, after dilution, it was extracted with ethyl acetate and washed using saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified using silica gel column chromatography (eluent: hexane / ethyl acetate = 10/1) and the title compound was obtained as a yellow oily substance.

**Step 4****Synthesis of t-butyl 2-(4-amino-2-fluoro-5-nitrophenyl) pyrrolidine-1-carboxylate**

To 2,2,2-trifluoro-N-(5-fluoro-2-nitro-4-(1-(trifluoroacetyl) pyrrolidin-2-yl) phenyl) acetamide 29 g dissolved in tetrahydrofuran 150 ml, were added 1N sodium hydroxide aqueous solution 150 ml under ice cooling, and the reaction liquor was stirred at room temperature for five hours. Furthermore, di t-butyl dicarbonate 23 ml was added to the reaction liquor and the reaction liquor was stirred for 30 minutes. The reaction liquor was diluted with ethyl acetate, and it was washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as a yellow solid

**Step 5****Synthesis of t-butyl 2-(4-amino-2-((2'-fluorobiphenyl-4-yl) oxy)-5-nitrophenyl) pyrrolidine-1-carboxylate**

To N,N-dimethylformamide 3 ml solution of t-butyl 2-(4-amino-2-fluoro-5-nitrophenyl) pyrrolidine-1-carboxylate 288 mg were added 2'-fluorobiphenyl-4-ol 200 mg and potassium carbonate 184 mg, and the reaction liquor was stirred overnight at 80°C. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 5/1) and the title compound was obtained as a yellow solid

#### Step 6

##### Synthesis of t-butyl 2-(4,5-diamino-2-((2'-fluorobiphenyl-4-yl) oxy) phenyl) pyrrolidine-1-carboxylate

To methanol 5 ml solution of t-butyl 2-(4-amino-2-((2'-fluorobiphenyl-4-yl) oxy)-5-nitrophenyl) pyrrolidine-1-carboxylate 410 mg was added development Raney nickel catalyst 1 ml, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for a whole day. The catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained as brown oily substance.

#### Step 7

##### Synthesis of 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole

To methanol 5 ml solution of t-butyl 2-(4,5-diamino-2-((2'-fluorobiphenyl-4-yl) oxy) phenyl) pyrrolidine-1-carboxylate 255 mg were added N-((1E)-pyridin-2-ylmethylene) aniline (1M methanol solution) 1.6 ml, and the reaction liquor was stirred at 90°C for a whole day. The reaction liquor was diluted with ethyl acetate, washed successively with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and 4 N hydrochloric acid-dioxane solution 5 ml was added to the obtained residue 332 mg, and the reaction liquor was stirred at room temperature for three hours. The solvent was eliminated by distillation under reduced pressure, and extraction was carried out with chloroform after dilution with saturated aqueous sodium bicarbonate. The organic layer was washed using saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was refined by silica gel column chromatography (eluent: chloroform-methanol / ammonia water solution = 20/1/0.1) and the title compound was obtained as a yellow oily substance.

**Step 8****Production of (2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl) methylamine**

To pyridine 1 ml solution of 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole 37 mg were added successively N-(t-butoxy carbonyl)-N-methylglycine 19 mg, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 24 mg, and the reaction liquor was stirred at room temperature for three hours. 4 N hydrochloric acid-dioxane solution 2 ml was added to the reaction liquor, and the reaction liquor was stirred at room temperature for one hour. The reaction liquor was diluted with chloroform, and it was made basic with saturated aqueous sodium bicarbonate. Thereafter, the organic layer was washed using saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 10/1) and the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.60-2.60 (6H, m), 2.80-3.05 (1H, m), 3.10-4.00 (4H, m), 5.20-5.60 (1H, m), 6.95-7.70 (11H, m), 7.75-7.95 (1H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 522 (M+H).

**Example 499****6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,3,4]-oxadiazol-2-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 6-(5-methyl-[1,3,4]-oxadiazol-2-yl) pyridin-3-ol, the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-2.40 (7H, m), 2.50-2.80 (3H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.00 (1H, m), 8.05-8.30 (1H, m), 8.30-8.50 (1H, m), 8.50-8.80 (2H, m), 10.50-11.00(1H, m).

ESI-MS (m/e): 482 (M+H).

**Example 500****6-(1-acetyl pyrrolidin-2-yl)-5-((6-([1,3,4]-oxadiazol-2-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 6-([1,3,4]-oxadiazol-2-yl) pyridin-3-ol, the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-2.40 (7H, m), 3.50-3.95 (2H, m), 5.05-5.50 (1H, m), 6.80-7.80 (4H, m), 7.80-8.00 (1H, m), 8.05-8.80 (5H, m), 10.50-11.00 (1H, m).

ESI-MS (m/e): 468 (M+H).

**Example 501****6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-(4-pyrimidin-2-yl phenoxy)-1H-benzimidazole**

Using 4-pyrimidin-2-yl phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.90 and 2.13 (total 3H, each s), 1.94-2.53 (4H, m), 3.62-3.80 (1H, m), 3.80-4.00 (1H, m), 5.38-5.46 (1H, m), 7.16-7.56 (6H, m), 7.95-8.04 (1H, m), 8.24-8.33 (1H, m), 8.46 (2H, d, J = 9.0 Hz), 8.70-8.79 (1H, m), 8.83-8.85 (2H, m).

ESI-MS (m/e): 477 (M+H).

**Example 502****1-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methyl) pyrrolidine-2,5-dione**

Using 1-((5-hydroxypyridin-2-yl) methyl) pyrrolidine-2,5-dione, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.46 (7H, m), 2.74-2.86 (4H, m), 3.53-3.90 (2H, m), 4.76-4.87 (2H, m), 5.18-5.48 (1H, m), 6.76-7.67 (5H, m), 7.80-7.91 (1H, m), 8.28-8.44 (2H, m), 8.57-8.67 (1H, m), 11.07-11.41 (1H, m).

ESI-MS (m/e): 511 (M+H).

**Example 503****6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-((6-(5-(trifluoromethyl) -[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-1H-benzimidazole**

Using 6-(5-(trifluoromethyl)-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.89-2.54 (7H, m), 3.84-4.01 (2H, m), 5.32-5.42 (1H, m), 7.20-7.80 (4H, m), 7.98-8.03 (1H, m), 8.24-8.37 (2H, m), 8.60-8.65 (1H, m), 8.73-8.80 (1H, m).

ESI-MS (m/e): 536 (M+H).

**Example 504****6-(1-acetyl pyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole**

Using 6-chloropyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H,

m), 7.80-8.50 (3H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 434 (M+H).

#### Example 505

6-(1-acetyl pyrrolidin-2-yl)-5-((6-bromopyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-bromopyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H, m), 7.70-8.00 (1H, m), 8.05-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 478, 480 (M+H).

#### Example 506

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methoxypyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methoxypyridin-3-ol, the title compound was obtained as yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.60 (7H, m), 3.50-4.10 (5H, m), 5.10-5.70 (1H, m), 6.60-7.70 (5H, m), 7.70-7.95 (1H, m), 7.95-8.10 (1H, m), 8.25-8.45 (1H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 430 (M+H).

#### Example 507

5-((2'-fluorobiphenyl-4-yl) oxy)-6-(1-(methanesulphonyl) pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazole

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 498 (Step 7), the title compound was obtained as colourless oil substance by the same process as in Example 178, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 2.70-3.00 (3H, m), 3.40-3.80 (2H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 529 (M+H).

#### Example 508

Methyl 2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxylate

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole

obtained in Example 498 (Step 7), the title compound was obtained as a colourless oily substance by the same process as in Example 181, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 3.40-3.80 (5H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.8 (1H, m).

ESI-MS (m/e): 509 (M+H).

#### Example 509

##### 2-(5-((2'-fluorobiphenyl-4-yl)

##### oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)-N,N-dimethylpyrrolidine-1-carboxamide

Using 5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained in Example 498 (Step 7), the title compound was obtained as a white solid in accordance with Example 336 (Step 1) (Step 2), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.20 (3H, m), 2.20-2.50 (1H, m), 2.72 (3H, s), 2.84 (3H, s), 3.40-3.80 (2H, m), 5.10-5.40 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 522 (M+H).

#### Example 510

##### 1-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl)

##### methyl) pyrrolidin-2-one

Using 1-((5-hydroxypyridin-2-yl) methyl) pyrrolidin-2-one, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.57 (11H, m), 3.33-3.89 (4H, m), 4.48-4.64 (2H, m), 5.20-5.51 (1H, m), 6.77-7.67 (5H, m), 7.77-7.90 (1H, m), 8.27-8.42 (2H, m), 8.56-8.66 (1H, m), 11.16-11.53 (1H, m).

ESI-MS (m/e): 497 (M+H).

#### Example 511

##### 6-(1-acetyl pyrrolidin-2-yl)-5-(4-(3-methyl-1H-[1,2,4]-triazol-5-yl)

##### phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(3-methyl-1H-[1,2,4]-triazol-5-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.76-2.82 (10H, m), 3.50-3.90 (2H, m), 5.13-5.59 (1H, m), 6.64-8.04 (8H, m), 8.23-8.64 (2H, m).

ESI-MS (m/e): 480 (M+H).

**Example 512**

6-(1-(difluoro acetyl) pyrrolidin -2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using difluoro acetic acid, the title compound was obtained as a white solid in accordance with Example 498 (Step 8), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.50 (4H, m), 3.60-4.20 (2H, m), 5.20-6.20 (2H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 529 (M+H).

**Example 513**

2-2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl acetate

Using acetoxy acetic acid, the title compound was obtained as a yellow oily substance in accordance with Example 498 (Step 8), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.40 (7H, m), 3.40-4.00 (2H, m), 4.05-4.80 (2H, m), 5.10-5.60 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 551 (M+H).

**Example 514**

(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methanol

To tetrahydrofuran 2 ml solution of ethyl 5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridine-2-carboxylate 90 mg obtained in Example 495 was added lithium aluminium hydride 20 mg under ice cooling, and the reaction liquor was stirred at 0°C for 30 minutes. The reaction liquor was diluted with chloroform, washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 4.70-4.85 (2H, m), 5.10-5.60 (1H, m), 6.80-7.70 (5H, m), 7.70-7.95 (1H, m), 8.30-8.50 (2H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 430 (M+H).

**Example 515**

2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol

To methanol solution 0.5 ml of 2-(2-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethyl acetate 11 mg obtained in Example 513 was added potassium carbonate 10 mg, and the reaction liquor was stirred at room temperature for one day. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup>60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-2.50 (4H, m), 3.40-4.20 (4H, m), 5.05-5.70 (1H, m), 6.90-8.10 (12H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 509 (M+H).

**Example 516**

6-(1-acetyl pyrrolidin-2-yl)-5-(((6-(fluoromethyl) pyridin-3-yl) oxy)-2-pyridin-2-yl)-1H-benzimidazole

To chloroform 1 ml solution of (5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) methanol 17 mg obtained in Example 514, bis (2-methoxyethyl) amino sulphur tri fluoride 0.050 ml was added under ice cooling, and the reaction liquor was stirred at 0°C for two hours. The reaction liquor was diluted with chloroform, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under the reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup>60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as slight yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.60 (3H, m), 6.80-7.70 (5H, m), 7.70-7.95 (1H, m), 8.30-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-11.00 (1H, m).

ESI-MS (m/e): 432 (M+H).

**Example 517**

6-(1-acetyl pyrrolidin-2-yl)-5-(((6-(3-methyl-[1,2,4]-oxadiazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl)-1H-benzimidazole

Using 6-(3-methyl [1,2,4]-oxadiazol-5-yl) pyridin-3-ol, the title compound was obtained as an



oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.65-2.57 (10H, m), 3.48-3.93 (5H, m), 5.17-5.52 (1H, m), 6.82-7.67 (7H, m), 7.80-7.91 (1H, m), 8.34-8.44 (1H, m), 8.57-8.67 (1H, m), 11.32-11.68 (1H, m).

ESI-MS (m/e): 482 (M+H).

#### Example 518

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1-methyl-1H-tetrazol-5-yl)phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1-methyl-1H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same method as in Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.83-2.40 (7H, m), 3.58-3.90 (2H, m), 4.15 and 4.19 (total 3H, each s), 5.16-5.48 (1H, m), 6.93-7.78 (7H, m), 7.80-7.91 (1H, m), 8.34-8.42 (1H, m), 8.56-8.65 (1H, m).

ESI-MS (m/e): 481 (M+H).

#### Example 519

5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)-N-methylpyridine-2-carboxamide

Using 5-hydroxy-N-methylpyridine-2-carboxamide, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.50 (7H, m), 2.90-3.10 (3H, m), 3.50-4.00 (2H, m), 5.05-5.50 (1H, m), 6.80-7.70 (3H, m), 7.70-8.00 (2H, m), 8.10-8.50 (3H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 457 (M+H).

#### Example 520

3-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)pyridin-2-yl)-1,3-oxazolidin-2-one

Using 3-(5-hydroxypyridin-2-yl)-1,3-oxazolidin-2-one, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.50 (7H, m), 3.50-4.00 (2H, m), 4.10-4.35 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (4H, m), 7.70-8.00 (1H, m), 8.10-8.50 (3H, m), 8.50-8.70 (1H, m), 10.70-11.10 (1H, m).

ESI-MS (m/e): 485 (M+H).

#### Example 521

6-(1-acetyl pyrrolidin-2-yl)-5-(6-methylpyridin-3-yl sulphanyl)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridine-3-thiol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.50 (10H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.00 (6H, m), 8.20-8.70 (3H, m).

ESI-MS (m/e): 430 (M+H).

**Example 522**5-(((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) nicotinic acid methyl ester

Using 5-hydroxy nicotinic acid methyl ester, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.89 and 2.14 (total 3H, each s), 1.96-2.20 (3H, m), 2.32-2.54 (11H, m), 3.63-3.90 (2H, m), 3.93 (3H, s), 5.37-5.41 (1H, m), 7.20-7.57 (3H, m), 7.92-8.03 (2H, m), 8.30 (1H, t, J = 8.4 Hz), 8.65-8.67 (1H, m), 8.74-8.78 (1H, m), 8.89-8.92 (1H, m).

ESI-MS (m/e): 458 (M+H).

**Example 523**6-(1-acetyl pyrrolidin-2-yl)-5-(((6-(methylthio) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylthio pyridin-3-ol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.70 (10H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.80-8.10 (6H, m), 8.20-8.50 (2H, m), 8.50-8.70 (1H, m), 10.70-11.10 (1H, m).

ESI-MS (m/e): 446 (M+H).

**Example 524**6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,3-dimethyl-1H-[1,2,4]-triazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,3-dimethyl-1H-[1,2,4]-triazol-5-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.79-2.2.53 (10H, m), 3.50-3.90 (5H, m), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m), 10.82-11.08 (1H, m).

ESI-MS (m/e): 494 (M+H).

**Example 525**

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,5-dimethyl-1H-[1,2,4]-triazol-3-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,5-dimethyl-1H-[1,2,4]-triazol-3-yl) phenol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.79-2.53 (10H, m), 3.50-3.90 (5H, in), 5.19-5.30 (1H, m), 6.87-7.66 (5H, m), 7.77-7.91 (1H, m), 7.96-8.10 (2H, m), 8.33-8.43 (1H, m), 8.56-8.67 (1H, m), 10.82-11.08 (1H, m).

ESI-MS (m/e): 494 (M+H).

**Example 526**

6-(1-acetyl pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester obtained in Example 338 (Step 2), pyrazine-2-carboxylic acid and 2'-fluorobiphenyl-4-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 3), (Step 5), a process based on these or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.50 (7H, m), 3.50-3.95 (2H, m), 5.10-5.60 (1H, m), 6.80-7.80 (10H, m), 8.50-8.90 (2H, m), 9.40-10.00 (1H, m), 10.50-11.20 (1H, m).

ESI-MS (m/e): 494 (M+H).

**Example 527**

6-(1-acetyl pyrrolidin-2-yl)-5-((5-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 5-chloro-3-pyridinol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.89 and 2.15 (total 3H, each s), 1.94-2.20 (3H, m), 2.29-2.49 (1H, m), 3.62-3.97 (2H, m), 5.32-5.40 (1H, m), 7.17-7.63 (4H, m), 7.94-8.04 (1H, m), 8.26-8.41 (3H, m), 8.73-8.79 (1H, m).

ESI-MS (m/e): 434 (M+H).

**Example 528**

1-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) pyridin-2-yl) pyrrolidin-2-one

Using 1-(5-hydroxypyridin-2-yl) pyrrolidin-2-one, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of

these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.79-2.43 (9H, m), 2.58-2.71 (2H, m), 3.53-3.89 (2H, m), 3.98-4.17 (2H, m), 5.21-5.57 (1H, m), 6.77-7.57 (4H, m), 7.74-8.66 (5H, m).

ESI-MS (m/e): 483 (M+H).

#### Example 529

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.60 (10H, m), 3.50-3.95 (2H, m), 5.20-5.60 (1H, m), 6.65-7.80 (4H, m), 8.20-8.40 (1H, m), 8.50-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.40 (1H, m).

ESI-MS (m/e): 415 (M+H).

#### Example 530

6-(1-acetyl pyrrolidin-2-yl)-5-((6-[[1,2,4]-oxadiazol-3-yl] pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-[[1,2,4]-oxadiazol-3-yl] pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.43 (7H, m), 3.57-3.92 (2H, m), 5.19-5.46 (1H, m), 6.98-8.43 (7H, m), 8.55-8.87 (3H, m), 10.53-10.74 (1H, m).

ESI-MS (m/e): 468 (M+H).

#### Example 531

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(1,3-oxazol-4-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(1,3-oxazol-4-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.89-2.20 (6H, m), 2.28-2.50 (1H, m), 3.62-4.00 (2H, m), 5.39-5.50 (1H, m), 7.12-7.53 (5H, m), 7.80-7.89 (2H, m), 7.93-8.04 (1H, m), 8.24-8.33 (3H, m), 8.70-8.79 (1H, m).

ESI-MS (m/e): 466 (M+H).

#### Example 532

6-(1-acetyl pyrrolidin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 526, a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.60 (7H, m), 3.50-3.95 (2H, m), 5.20-5.60 (1H, m), 6.65-8.30 (5H, m), 8.40-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.60 (1H, m).

ESI-MS (m/e): 435 (M+H).

#### Example 533

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.90-2.19 (6H, m), 2.27-2.51 (1H, m), 3.61-4.00 (2H, m), 4.43 and 4.44 (total 3H, each s), 5.38-5.46 (1H, m), 7.23 (2H, d, J = 8.6 Hz), 7.24-7.60 (2H, m), 8.11-8.19 (2H, m), 8.67-8.70 (1H, m), 8.77 (1H, brs), 9.46 (1H, d, J = 8.6 Hz).

ESI-MS (m/e): 482 (M+H).

#### Example 534

6-(1-acetyl pyrrolidin-2-yl)-5-((6-bromopyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-bromopyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.50 (7H, m), 3.60-3.95 (2H, m), 5.20-5.50 (1H, m), 6.80-8.40 (5H, m), 8.50-8.80 (2H, m), 9.50-9.70 (1H, m), 10.40-11.10 (1H, m).

ESI-MS (m/e): 479,481 (M+H).

#### Example 535

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol enantiomer A and enantiomer B

5-(1-acetyl-3-fluoro pyrrolidin-2-yl)-6-(4-(methanesulphonyl)

phenoxy)-2-pyridin-2-yl-1H-benzimidazole diastereomer B 10 mg obtained in Example 493 was optically resolved with column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 40/60/0.1, flow rate: 10 ml/min), and enantiomer A (retention time : 10.5 min) and enantiomer B (retention time : 19.0 min) were respectively obtained as white solid.

Enantiomer A

ESI-MS (m/e): 495 (M+H).

Enantiomer B

ESI-MS (m/e): 495 (M+H).

**Example 536**

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.88 and 2.02 (total 3H, each s), 1.93-2.20 (3H, m), 2.28-2.50 (1H, m), 3.60-4.00 (2H, m), 4.47 and 4.48 (total 3H, each s), 5.32-5.42 (1H, m), 7.22-7.70 (4H, m), 7.95-8.02 (1H, m), 8.25-8.32 (2H, m), 8.61-8.64 (1H, m), 8.73 (1H, brs).

ESI-MS (m/e): 482 (M+H).

**Example 537**

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(1-methyl-1H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.91 and 2.16 (total 3H, each s), 2.00-2.20 (3H, m), 2.38-2.55 (1H, m), 3.63-4.01 (2H, m), 4.50 and 4.51 (total 3H, each s), 5.35-5.44 (1H, m), 7.33-7.60 (2H, m), 7.66-7.73 (1H, m), 8.27-8.34 (1H, m), 8.65-8.67 (1H, m), 8.71-8.73 (1H, m), 8.78-8.80 (1H, m), 9.48-9.50 (1H, m).

ESI-MS (m/e): 483 (M+H).

**Example 538**

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.91-2.20 (6H, m), 2.33-2.52 (1H, m), 3.60-4.00 (2H, m), 4.48-4.90 (3H, m), 5.37-5.44 (1H, m), 7.22-7.68 (4H, m), 7.97-8.04 (1H, m), 8.19-8.23 (1H, m), 8.25-8.31 (1H, m), 8.55-8.59 (1H, m), 8.74 (1H, brs).

ESI-MS (m/e): 482 (M+H).

**Example 539**

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-1H-tetrazol-1-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 4-(5-methyl-1H-tetrazol-1-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.91 and 2.16 (total 3H, each s), 1.96-2.20 (3H, m), 2.33-2.54 (1H, m), 2.63 and 2.64 (total 3H, each s), 3.64-4.00 (2H, m), 5.38-5.43 (1H, m), 7.32-7.57 (4H, m), 7.61-7.68 (2H, m), 8.70-8.73 (1H, m), 8.78-8.80 (1H, m), 9.47-9.49 (1H, t).  
ESI-MS (m/e): 482 (M+H).

#### Example 540

6-(1-acetyl pyrrolidin-2-yl)-5-((6-[1H-pyrazol-1-yl] pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(1H-pyrazol-1-yl) pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.67-2.48 (7H, m), 3.50-3.92 (2H, m), 5.14-5.57 (1H, m), 6.41-6.50 (1H, m), 6.80-8.03 (7H, m), 8.17-8.67 (4H, m), 11.00-11.11.27 (1H, m).  
ESI-MS (m/e): 466 (M+H).

#### Example 541

6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-5-((6-[1H-[1,2,4]-triazol-1-yl] pyridin-3-yl) oxy)-1H-benzimidazole

Using 6-(1H-[1,2,4]-triazol-1-yl) pyridin-3-ol, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.62-2.45 (7H, m), 3.52-3.90 (2H, m), 5.20-5.55 (1H, m), 6.79-8.68 (10H, m), 9.02-9.13 (1H, m), 11.17-11.52 (1H, m).  
ESI-MS (m/e): 467 (M+H).

#### Example 542

5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer A and enantiomer B

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole 59.0 mg obtained by the same processes as in Example 162 (Step 2)-(Step 7) was optically resolved with column for optical resolution (CHIRALPAK AD 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: ethanol / 2-propanol / diethylamine 25/75/0.1, flow rate: 12-18 ml/min), and enantiomer A and enantiomer B were respectively obtained as pale yellow solid. (retention time : enantiomer A 13.5 min, enantiomer B 30.8 min, CHIRALPAK AD 4.6 mmφ x 250 cmL (made by Daicel Chemicals

Co.), mobile phase: ethanol / 2-propanol / diethylamine 25/75/0.1, flow rate: 1 ml/min).

#### Example 543

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)  
phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

To 5-(4-(2-methyl-2H-tetrazol-5-yl)

phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer A 24.7 mg obtained in Example 542 dissolved in chloroform 1 ml was added anhydrous acetic acid 0.006 ml, and the reaction liquor was stirred at room temperature for ten minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.90-2.20 (6H, m), 2.24-2.49 (1H, m), 3.66-4.00 (2H, m), 5.37-5.46 (1H, m), 7.12-7.60 (5H, m), 7.94-8.04 (1H, m), 8.04-8.20 (2H, m), 8.29 (1H, t, J = 8.2 Hz), 8.68-8.78 (1H, m).

ESI-MS (m/e): 481 (M+H).

#### Example 544

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)  
phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

To chloroform 1 ml solution of 5-(4-(2-methyl-2H-tetrazol-5-yl)

phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole enantiomer B 30.9 mg obtained in Example 542 was added acetic anhydride 0.007 ml, and thereafter, the reaction liquor was stirred at room temperature for 10 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

ESI-MS (m/e): 481 (M+H).

#### Example 545

5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl)  
phenoxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A, B, C and D

Using 5-methyl dihydrofuran-2(3H)-one, 4-component mixture of the title compound was obtained by a process same as Example 485, process based on this or combining these with the normal method. The obtained 4-component mixture 15 mg was column for optically resolution (CHIRAL-CEL OD-H 2 cmφ x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane/ethanol diethylamine = 80/20/0.1), and enantiomer A (retention time : 13.67 min), enantiomer B



(retention time : 15.24 min), enantiomer C (retention time : 18.96 min) and enantiomer D (retention time : 22.90 min) were respectively obtained as pale yellow solid.

**Enantiomer A**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.23-1.38 (3H, m), 1.50-2.57 (7H, m), 3.04 and 3.08 (3H, s), 4.24-4.60 (1H, m), 5.18-5.43 (1H, m), 6.92-7.83 (5H, m), 7.83-7.98 (3H, m), 8.34-8.43 (1H, m), 8.60-8.67 (1H, m), 10.84-11.33 (1H, m).

ESI-MS (m/e): 491 (M+H).

**Enantiomer B**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.22-2.20 (9H, m), 2.23-2.45 (1H, m), 3.04 and 3.08 (3H, s), 4.10-4.22 (1H, m), 5.09-5.23 (1H, m), 7.04-7.70 (5H, m), 7.83-7.97 (3H, m), 8.34-8.48 (1H, m), 8.61-8.69 (1H, m), 10.73-11.16 (1H, m).

ESI-MS (m/e): 491 (M+H).

**Enantiomer C**

ESI-MS (m/e): 491 (M+H).

**Enantiomer D.**

ESI-MS (m/e): 491 (M+H).

**Example 546**

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-ol, the title compound was obtained as a white solid in accordance with Example 526, a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.88-2.20 (6H, m), 2.21-2.31 (1H, m), 3.61-4.00 (2H, m), 4.46 and 4.47 (total 3H, each s), 5.34-5.44 (1H, m), 7.22-7.71 (3H, m), 8.18-8.25 (1H, m), 8.50-8.60 (1H, m), 8.65-8.70 (1H, m), 8.72-8.80 (1H, m), 9.44-9.47 (1H, m).

ESI-MS (m/e): 483 (M+H).

**Example 547**

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-(methoxymethyl)-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-(methoxymethyl)-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.90-2.20 (6H, m), 2.22-2.71 (1H, m), 3.53 (3H, s), 5.38-5.46 (1H, m), 5.96 and 5.97 (total 3H, each s), 7.20-7.56 (5H, m), 7.95-8.03 (1H, m), 8.17-8.22 (2H, m), 8.29 (1H, t, J = 8.0 Hz), 8.73-8.79 (1H, m).

ESI-MS (m/e): 511 (M+H).

#### Example 548

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(methoxymethyl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.43 (7H, m), 3.34-3.91 (5H, m), 4.45-4.59 (2H, m), 5.20-5.52 (1H, m), 6.86-7.67 (5H, m), 7.80-7.90 (1H, m), 8.29-8.48 (2H, m), 8.55-8.67 (1H, m), 10.87-11.27 (1H, m).

ESI-MS (m/e): 444 (M+H).

#### Example 549

2-(2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 168, a process based on this or a combination of these with a normal procedure using 5-(4-(2-methyl-2H-tetrazol-5-yl)

phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same processes as in Example 162 (Step 2)-(Step 7).

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.94-2.16 (3H, m), 2.23-2.48 (1H, m), 3.57-4.34 (4H, m), 4.43 and 4.44 (total 3H, each s), 5.27-5.52 (1H, m), 7.17-7.57 (5H, m), 7.94-8.04 (1H, m), 8.09-8.20 (2H, m), 8.24-8.32 (1H, m), 8.69-8.81 (1H, m).

ESI-MS (m/e): 497 (M+H).

#### Example 550

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide diastereomer B obtained in Example 493 and 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure..

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.82-2.43 (5H, m), 2.68 and 2.70 (3H, s), 3.64-4.40 (2H, m), 5.19-5.40 (1H, m), 5.42-5.64 (1H, m), 7.02-7.79 (4H, m), 7.80-7.92 (1H, m), 8.00-8.12 (1H, m), 8.35-8.42 (1H,

m), 8.60-8.75 (2H, m), 10.50-10.68 (1H, m).

ESI-MS (m/e): 500 (M+H).

#### Example 551

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(2-ethyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-ethyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.68 (3H, t, J = 7.2 Hz), 1.90 and 2.13 (total 3H, each s), 1.97-2.20 (3H, m), 2.29-2.53 (1H, m), 3.62-4.00 (2H, m), 4.73-7.79 (2H, m), 5.37-5.47 (1H, m), 7.19-7.60 (5H, m), 7.93-8.03 (1H, m), 8.10-8.20 (2H, m), 8.23-8.33 (1H, m), 8.74 (1H, brs)

ESI-MS (m/e): 495 (M+H).

#### Example 552

2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 184, a process based on this or a combination of these with a normal procedure using 5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazole obtained by the same process as in Example 162 (Step 2)-(Step 7).

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.97-2.10 (3H, m), 2.28-2.41 (1H, m), 3.52-3.63 (1H, m), 3.74-3.62 (1H, m), 5.26-5.41 (1H, m), 7.10-7.33 (1H, m), 7.23 (2H, d, J = 8.8 Hz), 7.44-7.61 (2H, m), 7.95-7.99 (1H, m), 8.12 (2H, d, J = 8.8 Hz), 8.27 (1H, d, J = 8.2 Hz), 8.72-8.73 (1H, m).

ESI-MS (m/e): 482 (M+H).

#### Example 553

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 550, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.83-2.17 (total 3H, each s), 2.10-2.40 (2H, m), 3.62-4.21 (2H, m), 4.41 and 4.42 (total 3H, each s), 5.23-5.43 (1H, m), 5.46-5.73 (1H, m), 7.10-7.65 (5H, m), 7.94-8.02 (1H, m), 8.03-8.17 (2H, m), 8.27 (1H, t, J = 8.8 Hz), 8.72 (1H, brs).

ESI-MS (m/e): 499 (M+H).

**Example 554**

5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridine-2-one enantiomer A and enantiomer B

Using 5'-hydroxy-2H-1,2'-bipyridin-2-one,

5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one 15.0 mg obtained by the same process as in Example 162 (Step 2)-(Step 7) was optically resolved with column for optical resolution (CHIRALPAK AD 2 cm $\phi$  x 25 cmL (made by Daicel Chemicals Co.), mobile phase: 2-propanol, flow rate: 10 ml/min), and enantiomer A (retention time: 23.6 min), enantiomer B (retention time: 50.7 min) were respectively obtained as pale yellow solid.

**Example 555**

5'-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer A

To 5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer A 6.5mg obtained in Example 554 dissolved in chloroform 1 ml was added acetic anhydride 0.003 ml, and thereafter the reaction liquor was stirred at room temperature for 30 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD)  $\delta$  : 1.91 and 2.16 (total 3H, each s), 1.94-2.20 (3H, m), 2.32-2.52 (1H, m), 3.63-3.98 (2H, m), 5.38-5.44 (1H, m), 6.49-6.54 (1H, m), 6.63-6.68 (1H, m), 7.23-7.58 (3H, m), 7.60-7.67 (2H, m), 7.77 (1H, dd, J = 8.8, 15.8 Hz), 7.87-7.93 (1H, m), 7.95-8.01 (1H, m), 8.27-8.31 (1H, m), 8.41 (1H, d, J = 2.9 Hz), 8.73 (1H, t, J = 4.7 Hz)  
ESI-MS (m/e): 493 (M+H).

**Example 556**

5'-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer B

To chloroform 1 ml solution of 5'-((2-pyridin-2-yl-6-pyrrolidine-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one enantiomer B 5.8 mg obtained in Example 554, acetic anhydride 0.003 ml was added, and thereafter the reaction liquor was stirred at room temperature for 30 minutes. The reaction solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound, one of chiral body was obtained as a white solid.

ESI-MS (m/e): 493 (M+H).

**Example 557**

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using

cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 4-(2-methyl-2H-tetrazol-5-yl) phenol, the title compound was obtained as a white solid in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.80-2.84 (2H, m), 1.94 and 2.25 (total 3H, each s), 3.90-4.30 (2H, m), 4.43 (3H, s), 5.28-5.50 (1H, m), 5.51-5.59 (1H, m), 7.18-7.64 (5H, m), 7.94-8.01 (1H, m), 8.12-8.18 (2H, m), 8.25-8.29 (1H, m), 8.70-8.77 (1H, m).

ESI-MS (m/e): 499 (M+H).

**Example 558**

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one, the title compound was obtained as yellow oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.50 (7H, m), 3.50-4.00 (2H, m), 3.90-4.25 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (7H, m), 7.80-8.00 (1H, m), 8.25-8.50 (1H, m), 8.50-8.80 (1H, m), 10.50-10.80 (1H, m).

ESI-MS (m/e): 484 (M+H).

**Example 559**

6-(1-acetyl pyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.72-2.59 (10H, m), 3.53-3.90 (2H, m), 5.20-5.55 (1H, m), 6.81-7.66 (5H, m), 7.78-7.92 (1H, m), 8.28-8.43 (2H, m), 8.55-8.66 (1H, m), 11.07-11.55 (1H, m).

ESI-MS (m/e): 414 (M+H).

**Example 560**

6-(1-acetyl pyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-pyrazin-2-yl pyridin-3-ol, the title compound was obtained as a yellow oily substance by the same process as in Example 483, a process based on this or a combination of these with a

normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.80-2.40 (7H, m), 3.60-3.90 (2H, m), 5.20-5.60 (1H, m), 7.00-7.80 (4H, m), 7.80-8.00 (1H, m), 8.30-8.50 (2H, m), 8.50-8.80 (4H, m), 9.50-9.70 (1H, m), 10.40-10.80 (1H, m).

ESI-MS (m/e): 478 (M+H).

#### Example 561

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole

Using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 2'-fluorobiphenyl-4-ol, the title compound was obtained as a yellow oily substance in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.80-2.80 (6H, m), 3.80-4.40 (2H, m), 5.05-5.50 (1H, m), 7.00-7.70 (11H, m), 7.75-7.95 (1H, m), 8.30-8.50 (1H, m), 8.50-8.75 (1H, m), 10.60-10.80 (1H, m).

ESI-MS (m/e): 511 (M+H).

#### Example 562

6-(cis-1-acetyl-4-fluoro pyrrolidin-2-yl)-5-(4-pyrazin-2-ylphenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 4-pyrazin-2-yl phenol, the title compound was obtained as yellow oily substance in accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.80 (6H, m), 3.80-4.40 (2H, m), 5.20-5.50 (1H, m), 7.00-7.70 (5H, m), 7.80-7.95 (1H, m), 7.95-8.20 (2H, m), 8.30-8.50 (2H, m), 8.50-8.80 (2H, m), 8.95-9.20 (1H, m), 10.60-10.80 (1H, m).

ESI-MS(m/e): 495 (M+H).

#### Example 563

N-((5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)pyridin-2-yl)methyl)acetamide

Using N-((5-hydroxypyridin-2-yl)methyl)acetamide, the title compound was obtained as oily substance by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.83-2.47 (10H, m), 3.54-3.90 (2H, m), 4.48-4.59 (2H, m), 5.21-5.50 (1H, m), 6.66-7.69 (6H, m), 7.79-7.91 (1H, m), 8.30-8.44 (2H, m), 8.54-8.69 (1H, m), 10.96-11.29 (1H, m).

ESI-MS (m/e): 471 (M+H).

#### Example 564

##### 6-(1-acetyl pyrrolidin-2-yl)-5-((6-fluoropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-fluoropyridin-3-ol, the title compound was obtained as yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.40-2.50 (7H, m), 3.50-4.00 (2H, m), 5.00-5.60 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.00-8.15 (1H, m), 8.25-8.50 (1H, m), 8.50-8.70 (1H, m), 10.60-10.80 (1H, m).

ESI-MS(m/e): 418[M+H].

#### Example 565

##### Cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

#### Step 1

##### Synthesis of cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

In accordance with Example 325 (Step 6), a process based on this or a combination of these with a conventional procedure, the title compound was obtained using cis-1-acetyl-2-(5-nitro-2-fluoro-4-((pyridine-2-carbonyl)-amino)-phenyl)-4-acetoxy-pyrrolidine obtained in Example 325 (Step 5) and 6-cyano-pyridin-3-ol.

#### Step 2

##### Production of

##### cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone enantiomer A and enantiomer B

Using cis-1-(4-fluoro-2-(6-(6-cyano-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone of racemic body obtained in (Step 1), the title compound was respectively obtained by the same process as in Example 333, a process based on this or a combination of these with a normal procedure.

#### Enantiomer A.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.91 (3H x 1/2, s), 2.22 (3H x 1/2, s), 2.32-2.67 (2H, m), 3.95-4.30 (2H, m), 5.27-5.47 (2H, m), 7.35-7.64 (3H, m), 7.85-7.92 (1H, m), 7.97-7.99 (1H, m), 8.29 (1H, t, J = 7.6 Hz), 8.60 (1H, d, J = 3.1 Hz), 8.74 (1H, s).

ESI-MS (m/e): 443 (M+H).

Enantiomer B.

ESI-MS (m/e): 443 (M+H).

#### Example 566

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)  
oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

##### Step 1

Synthesis of N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)  
pyridine-2-carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide diastereomer B300 mg obtained in Example 493 was optically resolved with column for optical resolution (CHIRAL CEL OD 2 cm $\phi$  x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / ethanol / diethylamine 50/50/0.1, flow rate: 10 ml/min), and enantiomer A and enantiomer were respectively obtained as yellow solid.

##### Step 2

Production of 6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)  
oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer A

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer A and 2'-fluorobiphenyl-4-ol, the title compound was obtained in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.82-2.43 (5H, m), 3.63-4.36 (2H, m), 5.25-5.70 (2H, m), 7.07-7.58 (11H, m), 7.74-7.90 (1H, m), 8.35-8.43 (1H, m), 8.58-8.68 (1H, m), 10.37-10.60 (1H, m).

ESI-MS (m/e): 511 (M+H).

#### Example 567

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl)  
oxy)-2-pyridin-2-yl-1H-benzimidazole enantiomer B

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 566 (Step 1), the title compound was obtained in accordance with Example 566 (Step 2), a process based on this or a combination of these with a conventional procedure.

ESI-MS(m/e): 511 (M+H).

#### Example 568



Cis-1-(4-fluoro-2-(6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 4-ethanesulfonyl-phenol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.90 (3H x 0.5, s), 2.22 (3H x 0.5, s), 2.25-2.75 (2H, m), 3.88-4.39 (2H, m), 5.24-5.48 (2H, m), 7.23-7.75 (5H, m), 7.90-8.02 (3H, m), 8.27-8.30 (1H, m), 8.73-8.75 (1H, m).  
ESI-MS (m/e): 509 (M+H).

**Example 569**

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidine-2-one enantiomer A

**Step 1**

Synthesis of t-butyl 2-(2-fluoro-4-((pyrazine-2-ylcarbonyl) amino) phenyl) pyrrolidine-1-carboxylate

In 2-(4-amino-2-fluoro-phenyl)-pyrrolidine-1-carboxylic acid t-butyl ester 3 g obtained in Example 338 (Step 2) dissolved in pyridine 5 ml were added successively pyrazine-2-carboxylic acid 1.5 g, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide • monohydrochloride 3.1 g, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as a yellow oily substance.

**Step 2**

Synthesis of N-(3-fluoro-4-pyrrolidin-2-yl phenyl) pyrazine-2-carboxamide dihydrochloride

To methanol 50 ml solution of t-butyl 2-(2-fluoro-4-((pyrazin-2-yl carbonyl) amino) phenyl) pyrrolidine-1-carboxylate 4.4 g was added 4 N hydrochloric acid-dioxane solution 50 ml, and the reaction liquor was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and the title compound was obtained as a yellow solid

**Step 3**

Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide

To N-(3-fluoro-4-pyrrolidin-2-yl phenyl) pyrazine-2-carboxamide dihydrochloride 4.3 g dissolved in pyridine 50 ml solution, acetic anhydride 1.5 ml was added, and the reaction liquor was stirred at room temperature for 20 minutes. The reaction liquor was diluted with chloroform, washed successively with water and saturated aqueous sodium chloride solution, and thereafter

dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 50/1) and the title compound was obtained as a yellow solid

#### Step 4

##### Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide

Fuming nitric acid 40 ml was added to N-(4-(1-acetyl pyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide 3.9 g under ice cooling, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was diluted with iced water, and it was made basic with saturated aqueous sodium bicarbonate, thereafter, extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform / methanol = 50/1) and the title compound was obtained as a yellow oily substance.

#### Step 5

##### Synthesis of N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer A and enantiomer B

N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide 500 mg was optically resolved with column for optical resolution (CHIRALPAK OD 2 cm $\phi$  x 25 cmL (made by Daicel Chemicals Co.), mobile phase: hexane / 2-propanol 1/1, flow rate: 15 ml/min), and enantiomer A (retention time: 18 min), enantiomer B (retention time: 25 min) were respectively obtained as pale yellow oily substance.

#### Step 6

##### Production of 3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one enantiomer A

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one and N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer A, the title compound, one of chiral body was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  : 1.00-2.40 (7H, m), 3.50-3.90(2H, m), 3.90-4.20 (2H, m), 4.40-4.60 (2H, m), 5.20-5.60 (1H, m), 6.80-7.70 (6H, m), 8.50-8.75 (2H, m), 9.50-9.70 (1H, m), 10.30-10.60 (1H, m).

ESI-MS (m/e): 485 (M+H).

**Example 570**

3-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one enantiomer B

Using 3-(4-hydroxyphenyl)-1,3-oxazolidin-2-one and N-(4-(1-acetyl pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide enantiomer B obtained in Example 569 (step 5), the title compound was obtained as a yellow oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure. ESI-MS (m/e): 485 (M+H).

**Example 571**

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(cyclopropyl sulfonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(cyclopropyl sulfonyl) phenol, the title compound was obtained as slight yellow solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.90-1.20 (2H, m), 1.20-1.40 (3H, m), 1.60-2.60 (7H, m), 3.50-4.00 (2H, m), 5.05-5.50 (1H, m), 7.00-8.20 (8H, m), 8.30-8.50 (1H, m), 8.55-8.80 (1H, m), 10.70-11.20 (1H, m).

ESI-MS(m/e): 503 (M+H).

**Example 572**

6-(1-acetyl pyrrolidin-2-yl)-5-(4-(methanesulfonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4-(ethanesulfonyl) phenol, the title compound was obtained as a white solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-1.40 (3H, m), 1.60-2.50 (7H, m), 3.00-3.20 (2H, m), 3.50-4.00 (2H, m), 5.10-5.50 (1H, m), 6.90-7.80 (5H, m), 7.80-8.00 (3H, m), 8.30-8.50 (1H, m), 8.50-8.75 (1H, m), 10.60-11.20 (1H, m).

ESI-MS (m/e): 491 (M+H).

**Example 573**

Cis-1-(4-fluoro-2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-ethanesulfonyl-pyridin-3-ol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.20-1.40 (3H, m), 1.90-2.30 (3H, m), 2.00-2.80 (2H, m), 3.20-3.50 (2H, m), 3.84-4.25 (2H, m), 5.27-5.45 (2H, m), 7.40-7.80 (4H, m), 8.00-8.20 (2H, m), 8.24-8.40 (1H,

m), 8.66 (1H, s), 8.80 (1H, brs).

ESI-MS (m/e): 510 (M+H).

#### Example 574

Cis-1-(4-fluoro-2-(6-(6-(5-methyl-[1,2,4]-oxadiazol-3-yl)  
pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained in accordance with Example 565 (Step 1), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.90-2.30 (3H, m), 2.00-2.80 (2H, m), 2.75 (3H, s), 3.84-4.40 (2H, m), 5.30-5.45 (2H, m), 7.25-7.80 (4H, m), 7.90-8.40 (3H, m), 8.55-8.68 (1H, m), 8.75 (1H, s).

ESI-MS (m/e): 500 (M+H).

#### Example 575

5-((6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)  
pyridine-2-carbonitrile

Using N-(4-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide enantiomer B obtained in Example 566 (Step 1) and 5-hydroxypyridine-2-carbonitrile, the title compound was obtained as an oily substance in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.54-2.45 (5H, m), 3.61-4.34 (2H, m), 5.09-5.54 (2H, m), 7.01-7.95 (6H, m), 8.34-8.47 (1H, m), 8.54-8.73 (2H, m), 10.66-10.79 (1H, m).

ESI-MS (m/e): 443 (M+H).

#### Example 576

6-(1-acetyl-3-fluoro pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)  
oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.54-2.45 (5H, m), 3.61-4.34 (2H, m), 5.09-5.54 (2H, m), 7.01-7.95 (6H, m), 8.34-8.47 (1H, m), 8.54-8.73 (2H, m), 10.66-10.79 (1H, m).

ESI-MS (m/e): 443 (M+H).

#### Example 577

6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl)  
oxy)-1H-benzimidazole

Using 6-pyrazin-2-yl pyridin-3-ol, the title compound was obtained as a straw-coloured oily

substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.05-2.50 (7H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 7.00-7.80 (3H, m), 8.20-8.45 (1H, m), 8.45-8.80 (5H, m), 9.50-9.70 (2H, m), 10.40-11.30 (1H, m).

ESI-MS (m/e): 479 (M+H).

#### Example 578

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-methylpyridin-3-ol and N-(4-(1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)pyridine-2-carboxamide obtained in Example 545, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.30 (7H, m), 2.30-2.70 (6H, m), 4.05-4.60 (1H, m), 5.20-5.60 (1H, m), 6.80-7.50 (4H, m), 7.70-7.90 (1H, m), 8.15-8.20 (1H, m), 8.25-8.40 (2H, m), 8.50-8.80 (1H, m).

ESI-MS (m/e): 428 (M+H).

#### Example 579

6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-chloropyridin-3-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 578, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20-2.60 (10H, m), 4.05-4.65 (1H, m), 5.10-5.50 (1H, m), 6.80-7.70 (4H, m), 7.80-8.10 (2H, m), 8.15-8.50 (2H, m), 8.60-8.80 (1H, m), 10.80-11.30 (1H, m).

ESI-MS (m/e): 448 (M+H).

#### Example 580

2-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl)oxy)pyridin-2-ylsulphanyl) ethanol

To N,N-dimethylformamide 1 ml solution of 6-(1-acetylpyrrolidin-2-yl)-5-((6-chloropyridin-3-yl)oxy)-2-pyridin-2-yl-1H-benzimidazole 20 mg obtained in Example 504 were added successively 2-mercaptoethanol 20 mg and potassium carbonate 10 mg, and the reaction liquor was stirred at 120°C for five hours. After cooling, the reaction liquor was diluted using saturated aqueous sodium bicarbonate, extracted with chloroform, and the organic layer was dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. The obtained residue was refined by preparative thin layer

chromatography (Kieselgel<sup>TM</sup> 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and the title compound was obtained as a white solid

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.10-2.50 (7H, m), 3.20-3.40 (2H, m), 3.50-4.00 (4H, m), 5.20-5.50 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.10-8.50 (2H, m), 8.50-8.70 (1H, m), 10.60-10.80 (1H, m).

ESI-MS (m/e): 476 (M+H).

#### Example 581

3-(5-((6-(1-acetyl pyrrolidin-2-yl)-2-pyridin-2-yl)-1H-benzimidazol-5-yl) oxy) pyridin-2-yl sulphanyl) propane-1-ol

Using 3-mercapto propane-1-ol, the title compound was obtained as a white solid by the same process as in Example 580, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.50 (7H, m), 3.20-3.40 (2H, m), 3.50-4.40 (6H, m), 5.20-5.60 (1H, m), 6.80-7.70 (5H, m), 7.80-7.95 (1H, m), 8.20-8.50 (2H, m), 8.50-8.70 (1H, m), 10.80-11.20 (1H, 1).

ESI-MS (m/e): 490 (M+H).

#### Example 582

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyridin-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-methyl picolinic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.86 and 2.10 (total 3H, each s), 1.92-2.43 (4H, m), 2.65 and 2.66 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.62-3.96 (2H, m), 5.25-5.32 (1H, m), 7.23 and 7.25 (total 2H, each d, J = 8.8 Hz), 7.20-7.58 (3H, m), 7.95 and 7.99 (total 2H, each d, J = 8.8 Hz), 8.38-8.42 (1H, m), 9.12-9.16 (1H, 1).

ESI-MS (m/e): 491 (M+H).

#### Example 583

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyrazine-2-yl)-5-(4-methanesulphonyl-phenoxy)-1H-benzimidazole

Using 5-methylpyrazine-2-carboxylic acid, the title compound was obtained as a straw-coloured solid by the same process as in Example 462, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.87-2.45 (7H, m), 2.66 and 2.67 (total 3H, each s), 3.14 and 3.16 (total 3H, each s), 3.63-4.00 (2H, m), 5.26-5.34 (1H, m), 7.20-7.61 (4H, m), 7.96 and 7.99 (total 2H, each d,

J = 8.8 Hz), 8.69 (1H, s), 9.32 and 9.34 (total 1H, each s).

ESI-MS (m/e): 492 (M+H).

#### Example 584

1-(4-((6-(1-acetyl-3-fluoropyridin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone

Using 1-(4-hydroxyphenyl) ethanone, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.62-2.60 (8H, m), 3.60-3.98, 4.04-4.33 (total 2H, each m), 5.11-5.56 (2H, m), 7.00-8.02 (8H, m), 8.33-8.48 (1H, m), 8.57-8.71 (1H, m), 10.76-11.09 (1H, m).

ESI-MS (m/e): 459 (M+H).

#### Example 585

6-(1-acetyl-3-fluoropyridin-2-yl)-5-((6-chloropyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-chloropyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 575, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.54-2.45 (5H, m), 3.60-4.35 (2H, m), 5.20-5.60 (2H, m), 6.90-7.00, 7.21-7.43, 7.60-7.93 (total 6H, eachm), 8.22-8.45 (2H, m), 8.58-8.70 (1H, m), 10.63-10.90 (1H, m).

ESI-MS (m/e): 452 (M+H).

#### Example 586

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.47 (7H, m), 2.57-2.73 (3H, m), 3.57-3.93 (2H, m), 5.21-5.48 (1H, m), 7.00-7.76 (3H, m), 7.96-8.14 (1H, m), 8.52-8.68 (3H, m), 9.54-9.65 (1H, m), 10.70-11.02, 11.53-10.66 (total 1H, each m).

ESI-MS (m/e): 483 (M+H).

#### Example 587

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(methanesulphonyl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using 6-(methanesulphonyl) pyridin-3-ol, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.51-2.47 (7H, m), 3.14-3.27 (3H, m), 3.58-3.92 (2H, m), 5.14-5.40 (1H, m), 7.03-7.79 (4H, m), 7.95-8.11 (1H, m), 8.48-8.71 (2H, m), 9.56-9.66 (1H, m), 10.65-10.194, 11.34-11.49 (total 1H, each m).

ESI-MS (m/e): 479 (M+H).

#### Example 588

1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone

Using 1-(4-hydroxyphenyl) ethanone, the title compound was obtained as an oily substance by the same process as in Example 570, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.53-2.61 (10H, m), 3.51-3.93 (2H, m), 5.14-5.47 (1H, m), 6.95-7.74 (4H, m), 7.88-8.02 (2H, m), 8.53-8.68 (2H, m), 9.54-9.66 (1H, m), 10.60-10.88, 11.43-11.54 (total 1H, each m)

ESI-MS(m/e): 442 (M+H).

#### Example 589

6-(1-acetyl pyrrolidin-2-yl)-5-((6-(difluoromethoxy) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 6-(difluoromethoxy) pyridine-3-ol, the title compound was obtained as pale yellow solid in accordance with Example 338 (Step 5), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.92 and 2.18 (total 3H, each s), 1.98-2.57 (4H, m), 3.65-4.00 (2H, m), 5.41-5.48(1H, m), 7.03 and 7.07 (total 1H, each d, J = 8.8 Hz), 7.00-7.72 (5H, m), 7.94-8.00 (1H, m), 8.08 (1H, s), 8.25 (1H, t, J = 7.4 Hz), 8.73 (1H, s).

ESI-MS (m/e): 466 (M+H).

#### Example 590

6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-5-(4-pyrazin-2-yl phenoxy)-1H-benzimidazole

Using 4-pyrazin-2-yl phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ : 1.10-2.60 (7H, m), 3.50-4.00 (2H, m), 5.20-5.60 (1H, m), 6.70-7.80 (4H, m), 7.90-8.20 (2H, m), 8.50-8.80 (4H, m), 8.95-9.20 (1H, m), 9.50-9.75 (1H, m), 10.60-11.40 (1H, m).

ESI-MS (m/e): 478 (M+H).



**Example 591****4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) benzonitrile**

Using 4-cyanophenol, the title compound was obtained as a yellow oily substance by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50-2.50 (7H, m), 3.50-3.90 (2H, m), 5.05-5.50 (1H, m), 6.65-7.80 (6H, m), 8.50-8.80 (2H, m), 9.50-9.70 (1H, m), 10.40-11.20 (1H, m).

ESI-MS (m/e): 425 (M+H).

**Example 592****Methyl 4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazine-2-yl-1H-benzimidazol-5-yl) oxy) benzoate**

Using methyl 4-hydroxybenzoate, the title compound was obtained as a yellow oily substance by the same process as in Example 526, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.50 (7H, m), 3.50-4.00 (5H, m), 5.10-5.60 (1H, m), 6.70-7.80 (4H, m), 7.90-8.20 (2H, m), 8.50-8.70 (2H, m), 9.50-9.70 (1H, m), 10.60-11.60 (1H, m).

ESI-MS (m/e): 458 (M+H).

**Example 593****2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide**

Using 2'-fluorobiphenyl-4-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 182, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.60-2.60 (4H, m), 3.20-4.20 (2H, m), 5.10-5.30 (1H, m), 5.60-5.90 (2H, m), 6.90-7.70 (11H, m), 7.90-8.10 (1H, m), 8.20-8.40 (1H, m), 8.60-8.80 (1H, m).

ESI-MS (m/e): 494 (M+H).

**Example 594****6-(1-acetyl pyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenoxy)-2-pyrazine-2-yl-1H-benzimidazole**

Using 4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenol, the title compound was obtained as a white solid by the same process as in Example 526, a process based on this or a combination of these with a normal procedure..

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60-2.80 (10H, m), 3.50-4.00 (2H, m), 5.15-5.60 (1H, m), 6.70-7.80 (5H, m), 7.90-8.20 (2H, m), 8.50-8.70 (1H, m), 9.50-9.70 (1H, m), 10.60-11.50 (1H, m).

ESI-MS (m/e): 482 (M+H).

**Example 595**

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

**Step 1**Synthesis of 2-fluoro-N-methoxy-N-methylbenzamide

To 2-fluoro-4-nitrobenzoic acid 10 g suspended in pyridine 80 ml were added N-methoxy-N-methylamine hydrochloride 5.79 g and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 12.4 g, and the reaction liquor was stirred overnight at room temperature. Pyridine was eliminated by distillation under reduced pressure, and thereafter, water was added. The obtained precipitate was recovered by filtration and, by washing with water and drying, the title compound was obtained as a straw-coloured solid.

**Step 2**Synthesis of 4-amino-2-fluoro-N-methoxy-N-methylbenzamide

To 2-fluoro-N-methoxy-N-methylbenzamide 10.84 g suspended in methanol 60 ml and water 30 ml, ammonium chloride 15.2 g and iron powder 8 g were added, and the reaction liquor was heated under reflux for three hours. The reaction liquor was filtered using celite, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained residue was diluted with ethyl acetate and was washed using water and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/2) and the title compound was obtained as brown oily substance.

**Step 3**Synthesis of N-(3-fluoro-4-((N-methoxy-N-methylamino) carbonyl) phenyl) pyrazine-2-carboxamide

To 4-amino-2-fluoro-N-methoxy-N-methylbenzamide 3.7 g dissolved in pyridine 20 ml were added pyrazine-2-carboxylic acid 2.56 g and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride 4.66 g, and the reaction liquor was stirred at room temperature for one hour. Pyridine was eliminated by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed using water and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and, by washing the obtained solid with mixed solvent of ethyl acetate and hexane, the title compound was obtained as a straw-coloured solid.

**Step 4**

Synthesis of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentynoyl)-3-fluorophenyl)  
pyrazine-2-carboxamide

To (3R)-3-(tert-butyl (dimethyl) silyl) oxy-1-butyne 4.92 g dissolved in tetrahydrofuran 80 ml was added n-butyllithium (2.46M hexane solution) 10.8 ml at -78°C, and the reaction liquor was stirred at the same temperature for one hour. N-(3-fluoro-4-((N-methoxy-N-methylamino) carbonyl) phenyl) pyrazine-2-carboxamide 2.7 g dissolved in tetrahydrofuran 60 ml was added at -78°C, and the reaction liquor was warmed to room temperature, and thereafter, it was stirred for two hours. Water was added to the reaction liquid and the liquid extracted with ethyl acetate and was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/1), and the title compound was obtained as a yellow solid

**Step 5**

Synthesis of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-pentynoyl)-3-fluorophenyl)  
pyrazine-2-carboxamide

To solution of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-2-pentynoyl)-3-fluorophenyl) pyrazine-2-carboxamide in mixture of 513 mg ethanol 20 ml and tetrahydrofuran 5 ml was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred under a hydrogen atmosphere for one hour 30 minutes. After eliminating the catalyst by filtration, the solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/1), and the title compound was obtained as a straw-coloured solid.

**Step 6**

Synthesis of N-(4-((4R)-1,4-dihydroxy pentyl)-3-fluorophenyl) pyrazine-2-carboxamide

To a solution of N-(4-((4R)-4-((tert-butyl (dimethyl) silyl) oxy)-pentynoyl)-3-fluorophenyl) pyrazine-2-carboxamide 340 mg in mixture of tetrahydrofuran 5 ml and methanol 10 ml was added sodium borohydride 89 mg, and the reaction liquor was stirred at room temperature for 30 minutes. The reaction liquor was concentrated down by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed with saturated ammonium chloride aqueous solution, and thereafter was dried with anhydrous magnesium sulphate. By eliminating under reduced pressure the solvent, crude product was obtained. To tetrahydrofuran 6 ml solution of the obtained crude product, tetrabutyl ammonium fluoride (1M tetrahydrofuran solution) 1.18 ml was added under ice cooling, and the reaction liquor was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1-ethyl acetate) and the title compound was obtained as a straw-coloured solid.

**Step 7****Synthesis of N-(4-((5S)-1-acetyl-5-methylpyrrolidin-2-yl)-3-fluorophenyl)  
pyrazine-2-carboxamide**

To N-(4-((4R)-1,4-dihydroxy pentyl)-3-fluorophenyl) pyrazine-2-carboxamide 147 mg suspended in chloroform 6 ml were added triethylamine 0.26 ml and methanesulphonyl chloride 0.11 ml, and the reaction liquor was stirred at room temperature for two hours. The reaction liquor was diluted with chloroform, washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. By eliminating the solvent by distillation under reduced pressure, crude product was obtained. To dimethylformamide 4 ml solution of the obtained crude product, sodium azide 30 mg was added under ice cooling, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, washed using water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. By eliminating the solvent under reduced pressure, crude product was obtained. To methanol 5 ml solution of the obtained crude product, copper sulfate pentahydrate 15 mg and sodium borohydride 52 mg were added, and the reaction liquor was stirred at room temperature for two hours. Sodium borohydride 35 mg was added, and the reaction liquor was stirred for 30 minutes. Further sodium borohydride 35 mg was added, and the reaction liquor was stirred for 30 minutes. The solvent was eliminated by distillation under reduced pressure and thereafter the residue was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. By eliminating the solvent by distillation under reduced pressure, crude product was obtained. Acetic anhydride 0.043 ml was added to chloroform 4 ml solution of the obtained crude product, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as straw-coloured oily substance.

**Step 8****Synthesis of N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)  
pyrazine-2-carboxamide**

To N-(4-((5S)-1-acetyl-5-methylpyrrolidin-2-yl)-3-fluorophenyl) pyrazine-2-carboxamide 59 mg, fuming nitric acid 1 ml was added at room temperature, and the reaction liquor was stirred at the same temperature for 30 minutes. The reaction liquor was diluted with chloroform and was washed using saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), ethyl acetate), and obtained the title compound as straw-coloured oily substance. (Rf : trans body > cis body)

## Step 9

Production of6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazine-2-yl-1H-benzimidazole

To N-methylpyrrolidinone 1 ml solution of N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide 10.4 mg were added 4-methansulphonyl-phenyl 9.2 mg, cesium carbonate 26.2 mg, and the reaction liquor was stirred at 90°C for one hour. Tin chloride (II) dihydrate 60 mg was added, and the reaction liquor was stirred at 90°C for one hour and at 100°C for two hours. To the reaction liquor were added ethyl acetate and saturated aqueous sodium bicarbonate, and precipitate was eliminated by filtration, thereafter extracted with ethyl acetate, and the organic layer was washed with water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and thereafter, it was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as straw-coloured oily substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.31 and 1.33 (total 3H, each d, J = 6.0 Hz), 1.55-2.60 (7H, m), 3.03-3.10 (3H, m), 4.25-4.62 (1H, m), 5.20-5.44 (1H, m), 7.01-7.68 (4H, m), 7.85-7.97 (2H, m), 8.57-8.69 (2H, m), 9.56-9.63 (1H, m).

ESI-MS (m/e): 492 (M+H).

## Example 596

N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxoethanamine

Using 2-methyl-2H-tetrazol-5-yl phenol, the title compound was obtained as a yellow oily substance by the same process as in Example 498 (Step 5)-(Step 8), a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80-2.50 (7H, m), 2.90-4.00 (4H, m), 4.30-4.50 (3H, m), 5.10-5.65 (1H, m), 7.10 (2H, m), 7.20-7.85 (3H, m), 7.80-7.95 (1H, m), 8.05-8.20 (2H, m), 8.30-8.50 (1H, m), 8.50-8.70 (1H, m).

ESI-MS (m/e): 510 (M+H).

## Example 597

6-(1-acetyl pyrrolidin-2-yl)-5-((4'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 4'-fluorophenyl-4-ol, the title compound was obtained as a straw-coloured solid by the same process as in Example 483, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.66-2.43 (7H, m), 3.44-3.92 (2H, m), 5.21-5.60 (1H, m), 6.80-7.67 (11H, m), 7.77-7.91 (1H, m), 8.30-8.43 (1H, m), 8.53-8.67 (1H, m), 10.89-11.43 (1H, m).

ESI-MS (m/e): 493 (M+H).

#### Example 598

6-(1-acetyl pyrrolidin-2-yl)-5-((3'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole

Using 3'-fluorophenyl-4-ol, the title compound was obtained as a straw-coloured solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.67-2.44 (7H, m), 3.44-3.92 (2H, m), 5.22-5.58 (1H, m), 6.92-7.68 (11H, m), 7.78-7.93 (1H, m), 8.33-8.45 (1H, m), 8.56-8.68 (1H, m), 10.88-11.38 (1H, m).

ESI-MS (m/e): 493 (M+H).

#### Example 599

2-(5-((6-cyanopyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide

Using 6-cyanopyridin-3-ol, the title compound was obtained as a white solid the same process as in Example 162 and Example 182, a process based on these or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD80D) δ : 1.80-2.20 (3H, m), 2.20-2.50 (1H, m), 3.40-3.60 (1H, m), 3.70-3.80 (1H, m), 4.80-5.30 (1H, m), 6.60-6.75 (2H, m), 7.20-7.70 (3H, m), 7.80-8.20 (3H, m), 8.20-8.30 (1H, m), 8.50-8.65 (1H, m), 8.70-8.80 (1H, m).

ESI-MS (m/e): 426 (M+H).

#### Example 600

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide obtained in Example 595 (Step 8) and

4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenol, the title compound was obtained as pale yellow solid the same process as in Example 595 (Step 9), a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.33 and 1.34 (total 3H, each d, J = 6.0 Hz), 1.55-2.60 (7H, m), 2.68 and 2.70 (total 3H, each s), 4.26-4.62 (1H, m), 5.28-5.49 (1H, m), 7.03-8.12 (4H, m), 8.40-8.69 (3H, m), 9.57-9.63 (1H, 1).

ESI-MS (m/e): 497 (M+H).

#### Example 601

6-(1-acetyl pyrrolidin-2-yl)-2-(5-methylpyrazine-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)-phenoxy)-1H-benzi

midazole

Using 4-(2-methyl-2H-tetrazol-5-yl) phenol and 5-methylpyrazine-2-carboxylic acid, the title compound was obtained as pale yellow solid the same process as in Example 306, a process based on this or a combination of these with a normal procedure.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD) δ : 1.88-2.48 (7H, m), 2.63 and 2.64 (total 3H, each s), 3.61-3.99 (2H, m), 4.41 and 4.42 (total 3H, each s), 5.37-5.4 (1H, m), 7.15-7.55 (2H, m), 7.17 (2H, d, J = 8.8 Hz), 8.08 and 8.11 (total 2H, each d, J = 8.8 Hz), 8.64 (1H, s), 9.27 and 9.29 (total 1H, each s).  
ESI-MS (m/e): 496 (M+H).

**Example 602**6-(1-acetyl-4-methylpyrrolidin-2-yl)-5-(4-(methanesulphonyl)  
phenoxy)-2-pyridin-2-yl-1H-benzimidazole**Step 1**Synthesis of N-(3-fluoro-4-(3-methyl-3-butenoyl) phenyl) pyridine-2-carboxamide

Using pyridine-2-carboxylic acid, (2-methyl-2-propen-1-yl) magnesium chloride (0.50M tetrahydrofuran solution) 9.89 ml was added under ice cooling to tetrahydrofuran 10 ml solution of N-(3-fluoro-4-((methoxy (methyl) amino) carbonyl) phenyl) pyridine-2-carboxamide 500 mg obtained in accordance with the same process as in Example 145 (Step 3), a process based on this or a combination of these with a conventional procedure. The reaction liquor was stirred under ice cooling for three hours, and thereafter the reaction liquor was discharged into water, and extraction was carried out with ethyl acetate and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 3/1) and the title compound was obtained.

**Step 2**Synthesis of N-(3-fluoro-4-(1-hydroxy-3-methyl-3-buten-1-yl) phenyl) pyridine-2-carboxamide

To N-(3-fluoro-4-(3-methyl-3-butenoyl) phenyl) pyridine-2-carboxamide 280 mg dissolved in methanol 5 ml solution, sodium borohydride 88.8 mg was added. The reaction liquor was stirred at room temperature for three hours, and thereafter, it was discharged into saturated ammonium chloride aqueous solution, and extraction was carried out with ethyl acetate and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 2/1) and the title compound was obtained.

**Step 3**Synthesis of N-(4-(1,4-dihydroxy-3-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide

Borane-methyl sulphide complex (1M dichloromethane solution) 1.20 ml was added under ice cooling to cyclohexene 0.082 ml dissolved in tetrahydrofuran 5 ml solution. The reaction liquor was stirred under ice cooling for ten minutes, and thereafter,

N-(3-fluoro-4-(1-hydroxy-3-methyl-3-buten-1-yl) phenyl) pyridine-2-carboxamide 301 mg dissolved in tetrahydrofuran 3 ml solution was added, and the reaction liquor was stirred at room temperature for one hour. 5N sodium hydroxide aqueous solution and 35 % hydrogen peroxide aqueous solution 0.50 ml were added successively to the reaction liquor and stirred at room temperature for ten minutes. The reaction liquor was discharged into saturated ammonium chloride aqueous solution and was extracted with acetic acid ethyl ester, and it was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 9/1) and the title compound was obtained.

#### Step 4

##### Synthesis of N-(3-fluoro-4-(4-methylpyrrolidin-2-yl) phenyl) pyridine-2-carboxamide

To N-(4-(1,4-dihydroxy-3-methylbutyl)-3-fluorophenyl) pyridine-2-carboxamide 236 mg dissolved in chloroform 5 ml solution, were added under ice cooling successively triethylamine 0.62 ml and methane sulphonyl chloride 0.213 ml, and the reaction liquor was stirred at room temperature for three hours. The reaction liquor was discharged into saturated aqueous sodium bicarbonate and was extracted with chloroform, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To dimethylformamide 3 ml solution of the obtained crude product, sodium azide 53.0 mg was added under ice cooling. The reaction liquor was stirred under ice cooling for 30 minutes and thereafter, stirred at room temperature for three hours. The reaction liquor was diluted with ethyl acetate and was washed using water, and thereafter was dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To methanol 4 ml solution of the obtained crude product, copper sulfate pentahydrate 20 mg and sodium borohydride 168 mg were successively added. The reaction liquor was stirred at room temperature for four hours, and thereafter, it was discharged into saturated aqueous sodium bicarbonate, and it was extracted with chloroform, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the crude product was obtained. To chloroform 3 ml solution of the obtained crude product, acetic anhydride 0.050 ml was added, and the reaction liquor was stirred at room temperature for 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/3), and the title compound was thereby obtained.

#### Step 5



Synthesis of N-(4-(1-acetyl-4-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl)  
pyridine-2-carboxamide

N-(3-fluoro-4-(4-methylpyrrolidin-2-yl) phenyl) pyridine-2-carboxamide 70.7 mg was dissolved in fuming nitric acid 1 ml, and the reaction liquor was stirred at room temperature for ten minutes. The reaction liquor was discharged into saturated aqueous sodium bicarbonate and was extracted with acetic acid ethyl ester, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2), and the title compound was obtained.

**Step 6**

Production of 6-(1-acetyl-4-methylpyrrolidin-2-yl)-5-(4-(methanesulphonyl)  
phenoxy)-2-pyridin-2-yl-1H-benzimidazole

To 2 ml N-methyl-pyrrolidinone solution of N-(4-(1-acetyl-4-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyridine-2-carboxamide 15 mg were added successively 4-(methanesulphonyl) phenol 13.4 mg and cesium carbonate 44.9 mg, and the reaction liquor was stirred at 90°C for one hour. After the addition of tin chloride dihydrate 43.8 mg to the reaction liquor, it was warmed to 100°C and was stirred for two hours. The reaction liquor was dissolved in ethyl acetate, and thereafter, it was washed with saturated aqueous sodium bicarbonate, and dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was refined by preparative thin layer chromatography (Kieselgel™ 60F<sub>254</sub>, Art5744 (Merck Co.), chloroform/methanol = 10/1), and obtained the title compound as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.80-2.63 (9H, m), 3.00-4.40 (2H, m), 3.05 and 3.08 (total 3H, each s), 5.03-5.43 (1H, m), 7.00-7.73 (5H, m), 7.83-7.98 (3H, m), 8.33-8.43 (1H, m), 8.62-8.70 (1H, m), 10.62-10.80 (1H, m).

ESI-MS (m/e): 491 (M+H).

**Example 603**

6-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl)  
oxy)-2-pyrazine-2-yl-1H-benzimidazole

Using N-(4-((2R,5S)-1-acetyl-5-methylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl) pyrazine-2-carboxamide obtained in Example 595 (Step 8) and 6-(methoxymethyl) pyridin-3-ol, the title compound was obtained as pale yellow oily substance in accordance with Example 595 (Step 9), a process based on this or a combination of these with a conventional procedure.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.10-2.22 (10H, m), 3.48 and 3.50 (total 3H, each s), 4.26-4.62 (1H, m), 4.57 and 4.59 (total 2H, each s), 5.33-5.52 (1H, m), 7.20-7.50 (4H, m), 8.40-8.70 (3H, m), 9.57-9.63 (1H, m).

ESI-MS (m/e): 459 (M+H).

#### Reference Example 1

##### [1,2,4] thiadiazole-5-carboxylic acid

To thio oxamic acid ethyl ester 1 g dissolved in chloroform 10 ml was added N,N-dimethylformamide dimethylacetal 2 ml, and the reaction liquor was stirred at room temperature for four hours. The solvent was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-1/2) and amidine body 1.1 g was obtained as red oily substance.

To amidine body 1.09 g and pyridine 0.95 ml dissolved in ethanol 18 ml was added hydroxylamine-O-sulfonic acid 721 mg dissolved in ethanol 20 ml, and the reaction liquor was stirred overnight at room temperature. The solvent was eliminated by distillation under reduced pressure and thereafter the residue was diluted with ethyl acetate and was washed with saturated aqueous sodium bicarbonate and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1) and [1,2,4] thiadiazole-5-carboxylic acid ethyl ester was obtained as straw-coloured oily substance. To the obtained [1,2,4] thiadiazole-5-carboxylic acid ethyl ester 300 mg dissolved in methanol 8 ml solution, 1N sodium hydroxide aqueous solution 5.7 ml was added, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the residue was neutralized using 2 N hydrochloric acid. The reaction liquor was concentrated down by distillation under reduced pressure, and thereafter the residue was washed with chloroform-methanol = 10/1, and the title compound was obtained as a white solid by eliminating the obtained organic layer under reduced pressure.

#### Reference Example 2

##### 2-difluoromethoxy-pyridin-3-ol

To 3-benzyloxy-2-hydroxypyridine 2 g suspended in acetonitrile 40 ml were added sodium carbonate 2.1 g and difluoro fluorosulfonyl acetic acid 1.24 ml, and the reaction liquor was stirred at room temperature for one hour, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was diluted with ethyl acetate and was washed using water and thereafter, dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 9/1-4/1) and difluoromethoxy body was obtained as straw-coloured oily substance. To difluoromethoxy body 2.38 g dissolved in methanol 25 ml solution, 10 % palladium-carbon catalyst 500 mg was added, and the reaction liquor was stirred at room temperature under a hydrogen atmosphere for one hour. The catalyst

was eliminated by filtration by celite, and, by eliminating the solvent under reduced pressure, the title compound was obtained as light purple oily substance.

### Reference Example 3

#### 6-methanesulphonyl-pyridin-3-ol

In 3-bromo-6-methanesulphonyl-pyridine 4.72 g dissolved in dimethylsulfoxide 8 ml were added bis (pinacolate) diboron 6.6 g, potassium acetate 5.9 g and (1,1'-bis (diphenylphosphino) ferrocene) dichloroparadium (II) dichloromethan complex 980 mg, and the reaction liquor was stirred at 80°C for two hours. Acetic acid ethyl ester and water were added to the reaction liquor, insolubles substance were eliminated by filtration with celite and thereafter, the organic layer was separated. The organic layer was washed using water and saturated aqueous sodium chloride solution, and thereafter dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. 5N sodium hydroxide aqueous solution 60 ml and 30 % hydrogen peroxide water 30 ml were added to tetrahydrofuran 200 ml solution of the obtained residue at 0°C, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with diethyl ether and thereafter washed using water. The aqueous layer was acidified with 5 N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was dried with anhydrous magnesium sulphate, and the solvent was eliminated by distillation under reduced pressure. By washing the obtained residue with mixed solvent of chloroform and hexane, the title compound was obtained as a brown solid.

### Reference Example 4

#### 6-ethanesulfonyl-pyridin-3-ol

Using 3-chloro-6-ethane sulfonyl-pyridine, the title compound was obtained the same method as in Reference Example 3, process base on this or by combining these with the normal method.

### Reference Example 5

#### (2R,4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide

#### Step 1

##### Synthesis of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester

To (2R,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 3.61 g dissolved in dimethylformamide 60 ml were added successively tert-butyl diphenyl silyl chloride 2.32 g and imidazole 2.32 g, and the reaction liquor was stirred overnight at room temperature. The reaction liquor was diluted with ethyl acetate, washed successively with saturated ammonium chloride aqueous solution, saturated aqueous sodium chloride solution, and thereafter dried with anhydrous sodium sulphate. The solvent was eliminated by distillation under reduced pressure,

and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/2) and the title compound was obtained.

#### Step 2

##### Synthesis of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

To (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2.62 g dissolved in pyridine 30 ml solution obtained in (Step 1) were added successively 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride 1.50 g and O,N-dimethyl hydroxylamine hydrochloride 761 mg, and the reaction liquor was stirred overnight at room temperature. The solvent of the reaction liquor was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1) and the title compound was obtained.

#### Step 3

##### Synthesis of (2R,4R)-4-hydroxy-2-methoxy-methyl-carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester

To tetrahydrofuran 30 ml solution of (2R,4R)-4-(tert-butyl-diphenyl-silanyl oxy)-2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester 2.04 g obtained in (Step 2) was added tetrabutyl ammonium fluoride (1M tetrahydrofuran solution) 7.46 ml, and the reaction liquor was stirred at room temperature for 20 minutes. The solvent of the reaction liquor was eliminated by distillation under reduced pressure and the obtained residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/3) and the title compound was obtained.

#### Step 4

##### Production of (2R,4R)-4-hydroxy-pyrrolidine-2-carboxylic acid methoxy-methyl amide

To ethanol 20 ml solution of (2R,4R)-4-hydroxy-2-methoxy-methyl-carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester 600 mg obtained in (Step 3) was added 10 % palladium-carbon catalyst 100 mg, and the reaction liquor was stirred overnight under a hydrogen atmosphere. The reaction liquor was stirred under hydrogen atmosphere over night. The catalyst was eliminated by filtration with celite, thereafter the solvent was eliminated by distillation under reduced pressure, and the title compound was thereby obtained.

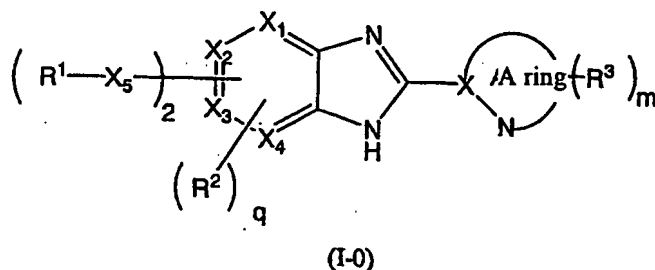
#### Possible Commercial Applications

The substituted benzimidazole derivatives in accordance with this invention and represented by aforesaid formula (I-O) demonstrate excellent glucokinase activity and therefore are useful in the

field of medicine, treatment and prevention of diabetes, diabetes complications and obesity.

## Patent Claims

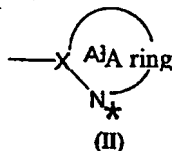
1. A compound represented by Formula (I-0), or pharmacologically acceptable salts thereof



[wherein, X denotes a carbon atom or nitrogen atom,

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> each independently denote carbon atom or nitrogen atom,

A ring denotes a 5-6 membered nitrogen containing heteroaromatic ring represented by formula (II)



which may contain 1-3 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (excluding the nitrogen atom represented by N\* in formula II), or a bicyclic ring in which the said nitrogen containing heteroaromatic ring and phenyl or pyridyl are condensed,

R<sup>1</sup> denotes aryl or a 4-10 membered monocyclic or bicyclic heterorings containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom in the ring (the said R<sup>1</sup> may be each independently substituted with 1 to 3 R<sup>4</sup>, moreover, when the said heteroring is an aliphatic heteroring, it may contain 1 or 2 double bonds),

R<sup>2</sup> each independently denote hydroxy, formyl, -CH<sub>3</sub>-F<sub>6</sub>, -OCH<sub>3</sub>-F<sub>6</sub>, amino, CN, halogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>1-4</sub>OH,

R<sup>3</sup> denotes -C<sub>1-6</sub> alkyl, -(CH<sub>2</sub>)<sub>1-6</sub>-OH, -C(O)-OC<sub>1-6</sub> alkyl, -(CH<sub>2</sub>)<sub>1-6</sub>-OC<sub>1-6</sub> alkyl, -(CH<sub>2</sub>)<sub>1-6</sub>-NH<sub>2</sub>, cyano, -C(O)-C<sub>1-6</sub> alkyl, halogen, -C<sub>2-6</sub> alkenyl, -OC<sub>1-6</sub> alkyl, -COOH, -OH or oxo,

R<sup>4</sup> each independently,

-C<sub>1-6</sub> alkyl (the said alkyl may be substituted with the same or different 1 to 3 hydroxy, halogen,

-OC(O)-C<sub>1-6</sub> alkyl (the said alkyl may be substituted with 1 to 3 halogen), or -OC<sub>1-6</sub> alkyl)

-C<sub>3-7</sub> cycloalkyl,

-C<sub>2-6</sub> alkenyl,

-C(O)-N(R<sup>51</sup>)R<sup>52</sup>,

-S(O)<sub>2</sub>-N(R<sup>51</sup>)R<sup>52</sup>,

-O-C<sub>1-6</sub> alkyl (the said C<sub>1-6</sub> alkyl may be substituted with halogen or N(R<sup>51</sup>)R<sup>52</sup>),

-S(O)<sub>0-2</sub>-C<sub>1-6</sub> alkyl,

-C(O)-C<sub>1-6</sub> alkyl (the said C<sub>1-6</sub> alkyl may be substituted with halogen, amino, CN, hydroxy, -O-

C<sub>1-6</sub> alkyl, -CH<sub>3-4</sub>F<sub>1-3</sub>, -OC(O)-C<sub>1-6</sub> alkyl, -N (C<sub>1-6</sub> alkyl)C(O)O-C<sub>1-6</sub> alkyl, -NH-C(O)O-C<sub>1-6</sub> alkyl, phenyl, -N(R<sup>51</sup>)R<sup>52</sup>-NH-C(O)-C<sub>1-6</sub> alkyl, -N (C<sub>1-6</sub> alkyl)-C(O)-C<sub>1-6</sub> alkyl or -NH-S(O)<sub>0-2</sub>-C<sub>1-6</sub> alkyl),

-C(S)-C<sub>3-7</sub> cycloalkyl,

-C(S)-C<sub>1-6</sub> alkyl,

-C(O)-O-C<sub>1-6</sub> alkyl,

-(CH<sub>2</sub>)<sub>0-4</sub>-N(R<sup>53</sup>)-C(O)-R<sup>54</sup>,

-N(R<sup>53</sup>)-C(O)-O-R<sup>54</sup>,

-C(O)-aryl (the said aryl may be substituted with halogen),

-C(O)-heteroaromatic ring,

-C(O)-aliphatic hetero ring,

hetero ring (the said hetero ring may be substituted with -C<sub>1-6</sub> alkyl (the said -C<sub>1-6</sub> alkyl may be substituted with halogen or -O-C<sub>1-6</sub> alkyl),

phenyl (the said phenyl may be substituted with halogen, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl),

halogen, CN, formyl, COOH, amino, oxo, hydroxy, hydroxy amidino or nitro,

R<sup>51</sup> and R<sup>52</sup> each independently denote hydrogen atom, -C<sub>1-6</sub> alkyl,

or 4-7 membered hetero ring formed by linking nitrogen atom, R<sup>51</sup> and R<sup>52</sup> together,

R<sup>53</sup> denotes a hydrogen atom or -C<sub>1-6</sub> alkyl,

R<sup>54</sup> denotes -C<sub>1-6</sub> alkyl or,

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R<sup>53</sup> and R<sup>54</sup>, and -N-C(O)- together or

4-7 membered nitrogen-containing aliphatic hetero ring formed by linking the alkyl of R<sup>53</sup> and R<sup>54</sup>, and -N-C(O)-O- together (the said aliphatic hetero ring may be substituted with oxo, and moreover, the said aliphatic hetero ring may contain 1 or 2 double bonds in the ring),

X<sub>5</sub> denotes -O-, -S-, -S(O)-, -S(O)<sub>2</sub>-, single bond or -O-C<sub>1-6</sub> -alkyl",

a denotes, each independently, an integer of 1, 2 or 3,

q denotes an integer of 0-2,

m denotes an integer of 0-2]

(wherein the following cases were excluded:

the case wherein one of X<sub>5</sub> is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-, and the other X<sub>5</sub> is single bond, and also R<sup>1</sup> is aryl or nitrogen-containing aromatic heteroring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said aryl may be substituted with 1-3 R<sup>4</sup>),

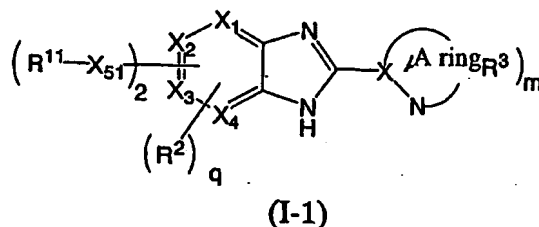
the case wherein both X<sup>5</sup> are single bonds, or

the case wherein both R<sup>1</sup> are aliphatic heteroring).

2. A compound in accordance with Claim 1 or pharmacologically acceptable salts thereof, wherein X<sub>1</sub> to X<sub>4</sub> are all carbon atoms.

3. A compound in accordance with Claim 1 or pharmacologically acceptable salts thereof, wherein  $X_5$  is -O-, -S-, -S(O)-, -S(O)<sub>2</sub>- or single bond.

4. A compound in accordance with Claim 1 represented by formula (I-1) or pharmacologically acceptable salts thereof



[in the formula,  $R^{11}$  denotes phenyl which may be substituted with 1-3  $R^4$  or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ), and also

$X_{51}$  denotes -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-, and the other symbols are the same as above].

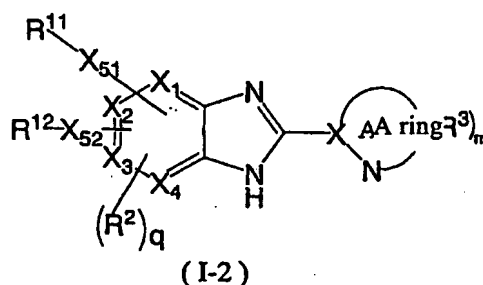
5. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein both  $R^{11}$  are phenyl which may be substituted with 1-3  $R^4$ .

6. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein both  $R^{11}$  are 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ).

7. A compound in accordance with Claim 4 or pharmacologically acceptable salts thereof, wherein one of the  $R^{11}$  is phenyl which may be substituted with 1-3  $R^4$  and also the other  $R^{11}$  is 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ).

8. A compound in accordance with Claim 1 represented by formula (I-2) or pharmacologically acceptable salts thereof





[in the formula,  $R^{11}$  denotes phenyl which may be substituted with 1-3  $R^4$  or 5 or 6-membered nitrogen-containing heteroaromatic ring containing 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing heteroaromatic ring may be substituted with 1-3  $R^4$ ),

$R^{12}$  denotes 4 to 7-membered nitrogen-containing heteroring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-4 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said  $R^{12}$  may be substituted with 1-3  $R^4$ , and moreover, when the said hetero ring is an aliphatic hetero ring, it may contain 1 or 2 double bonds),

$X_{51}$  is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-,

$X_{52}$  is -O-, -S-, -S(O)-, -S(O)<sub>2</sub>- or single bond, and the other symbols are the same as above].

9. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein  $R^{12}$  is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3  $R^4$ . And also  $X_{52}$  is a single bond, or

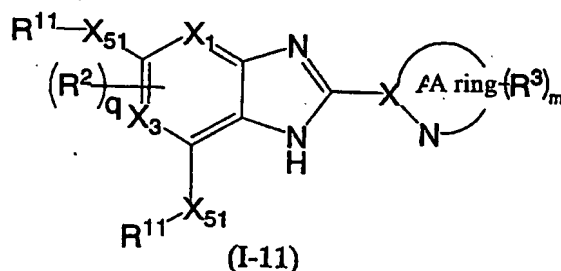
$R^{12}$  is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid  $R^4$ . And also  $X_{52}$  is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-.

10. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein  $R^{12}$  is 4 to 7-membered nitrogen-containing saturated aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom (the said nitrogen-containing aliphatic hetero ring may be substituted with 1-3  $R^4$ . And also  $X_{52}$  is a single bond.

11. A compound in accordance with Claim 8 or pharmacologically acceptable salts thereof, wherein  $R^{12}$  is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid  $R^4$ . And also  $X_{52}$  is -O-, -S-, -S(O)- or -S(O)<sub>2</sub>-.

12. A compound in accordance with aforesaid (8) or pharmacologically acceptable salts thereof, wherein in formula (I-2),  $R^{12}$  is 5 to 7-membered nitrogen-containing aliphatic hetero ring having as hetero atom constituting the hetero ring at least one nitrogen atom and also as other hetero atom, 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom and moreover containing 1 or 2 double bonds in the ring (the said 5 to 7-membered nitrogen-containing hetero ring may be substituted with 1-3 of aforesaid  $R^4$ . And also  $X_{52}$  is -O-.

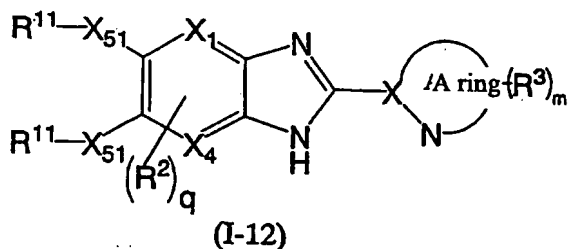
13. A compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-11)



(each symbol is the same as above).

14. A compound in accordance with Claim 13 or pharmacologically acceptable salts thereof, wherein both  $X_{51}$  are -O-.

15. A compound or the pharmacologically acceptable salts thereof wherein formula (I-1) is represented by formula (I-12)

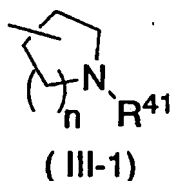


(each symbol is the same as above).

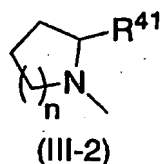
16. A compound in accordance with Claim 15 or pharmacologically acceptable salts thereof,

wherein both  $X_{S1}$  are -O-.

17. A compound in accordance with Claim 10 or pharmacologically acceptable salts thereof, wherein  $R^{12}$  is formula (III-1)



or formula (III-2)



[wherein,  $n$  denotes an integer of 1-3, and  $R^{41}$  denotes the group same as the aforesaid  $R^4$ ].

18. A compound in accordance with any one of Claims 1 to 17 or pharmacologically acceptable salts thereof, wherein the A ring is thiazolyl, imidazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyridazinyl, pyrazolyl or pyrimidinyl wll of which may be substituted with 1-3 of aforesaid  $R^4$ .

19. A compound or pharmacologically acceptable salts thereof, wherein the compound represented by formula (I-0) is

5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-6-(2-carbamoyl-phenoxy)-1H-benzimidazole,  
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimida  
zole,

5-(2-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimida  
zole,

5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-  
1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-  
1H-benzimidazole,

5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-(1-methyl-1H-  
-pyrazol-3-yl)-1H-benzimidazole,

5-(2-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,

5-(2-fluoro-phenoxy)-2-(1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazo

le,  
5-(2,3-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2,4-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole  
,  
5-(2,5-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole  
,  
5-(2,6-difluoro-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole  
,  
5-(2,6-difluoro-phenoxy)-2-(1-methyl-1H-pyrazol-3-yl)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
le,  
5-(2-fluoropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
le,  
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
le,  
5-(2-chloropyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
le,  
5-(2-cyanopyridin-3-yloxy)-6-(6-ethanesulfonylpyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
e,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(2-difluoromethoxy-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(2,6-difluoro-phenoxy)-2-pyridin-2-yl-6-(6-methanesulphonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
e,  
5-(2-fluoro-6-cyano-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyridin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-6-carbamoyl-phenoxy)-2-pyrazin-2-yl-6-(4-ethanesulfonyl-phenoxy)-1H-benzimidazole

ole,  
5-(2-fluoro-6-cyano-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-fluoro-6-(tetrazol-5-yl)-phenoxy)-2-pyrazin-2-yl-6-(6-ethanesulfonyl-pyridin-3-yloxy)-1H-benzimidazole,  
5-(2-difluoromethoxypyridin-3-yloxy)-6-(3-chloro-4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2-fluoro-phenoxy)-2-(pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
,  
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
,  
4-(1-methyl-2-oxo-1,2-dihydro-pyridin-3-yloxy)-6-(4-ethanesulfonyl-phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2,6-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-(1H-pyrazol-3-yl)-1H-benzimidazole,  
4-(2-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
4-(2,3-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
,  
4-(2,5-difluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
,  
4-(2-cyano-6-fluoro-phenoxy)-6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-1H-benzimidazole,  
4-(2-cyano-6-fluoro-phenoxy)-6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-1H-benzimidazole,  
1-(2-(6-(5-bromo-pyridin-2-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-(4-hydroxymethyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-ethanone,  
1-(2-(6-[4-methanesulphonyl-phenoxy]-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-et

hanone,  
2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidine-1-carbox  
amide,  
2-hydroxy-1-(2-(6-(4-methanesulphonyl-1-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrro  
lidin-1-yl)-ethanone,  
1-(2-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl  
)-ethanone,  
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-et  
hanone,  
2-fluoro-1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidi  
n-1-yl)-ethanone,  
5-(6-(1-acetyl-pyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridine-2-carbonitrile,  
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-1-yl)-2-  
methylamino-ethanone,  
1-(2-(6-(4-methanesulphonyl-phenoxy)-2-(1H-pyrazol-3-yl)-3H-benzimidazol-5-yl)-pyrrolidin-1-  
yl)-ethanone,  
1-(4-fluoro-2-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidi  
n-1-yl)-ethanone,  
N-(5-(6-[1-acetyl-pyrrolidin-2-yl]-2-pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-2-yl)-aceta  
mide,  
1-(2-(2-(5-bromo-pyridin-2-yl)-6-(4-methanesulphonyl-phenoxy)-3H-benzimidazol-5-yl)-pyrroli  
din-1-yl)-ethanone,  
N-(2-(2-[6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl]-pyrrolidin-1-yl  
) -2-oxo-ethyl)-acetamide,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(methoxymethyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole •  
mono trifluoroacetate,  
1-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)  
pyridine-2(1H)-one,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)  
oxy)-2-pyridin-2-yl-1H-benzimidazole,  
(2-(2-(5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl)  
pyrrolidin-1-yl)-2-oxoethyl) methylamine,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl)  
oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl)  
phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
5-(1-acetyl-3-fluoropyrrolidin-2-yl)-6-(4-(methanesulphonyl)  
phenoxy)-2-pyridin-2-yl-1H-benzimidazole,

6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
5-(1-acetyl-5-methylpyrrolidin-2-yl)-6-(4-(methanesulphonyl) phenoxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(2-methyl-2H-tetrazol-5-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-(6-(methoxymethylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanol,  
2-(5-(4-(2-methyl-2H-tetrazol-5-yl) phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidine-1-carboxamide,  
5'-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy)-2H-1,2'-bipyridin-2-one,  
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyridin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-methylpyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
6-(1-acetyl-3-fluoropyrrolidin-2-yl)-5-((2'-fluorobiphenyl-4-yl) oxy)-2-pyridin-2-yl-1H-benzimidazole,  
3-(4-((6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl)-1,3-oxazolidin-2-one,  
6-(1-acetylpyrrolidin-2-yl)-2-pyrazin-2-yl-5-((6-pyrazin-2-yl pyridin-3-yl) oxy)-1H-benzimidazole,  
6-(1-acetylpyrrolidin-2-yl)-5-((6-(5-methyl-[1,2,4]-oxadiazol-3-yl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,  
1-(4-((6-(1-acetyl pyrrolidin-2-yl)-2-pyrazin-2-yl-1H-benzimidazol-5-yl) oxy) phenyl) ethanone,  
6-(1-acetylpyrrolidin-2-yl)-5-(4-(5-methyl-[1,2,4]-oxadiazol-3-yl) phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-(4-methanesulphonyl-phenoxy)-2-pyrazin-2-yl-1H-benzimidazole,  
N-methyl-2-(2-(5-(4-[2-methyl-2H-tetrazol-5-yl] phenoxy)-2-pyridin-2-yl-1H-benzimidazol-6-yl) pyrrolidin-1-yl)-2-oxo ethanamine,  
6-(1-acetyl-5-methylpyrrolidin-2-yl)-5-((6-(methoxymethyl) pyridin-3-yl) oxy)-2-pyrazin-2-yl-1H-benzimidazole,

1-(1-(6-(4-methanesulphonyl-phenoxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone,  
1-(1-(6-(6-methanesulphonyl-pyridin-3-yloxy)-2-pyridin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone,  
1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-pyrrolidin-2-yl)-ethanone, or  
1-(1-(6-(6-ethanesulfonyl-pyridin-3-yloxy)-2-pyrazin-2-yl-3H-benzimidazol-5-yl)-4-fluoro-pyrrolidin-2-yl)-ethanone.

20. A medicinal composition comprising the following (1)-(3) to be used for therapy, prevention and/or delay of onset of type II diabetes mellitus;

- (1) a compound in accordance with any one of Claims 1-19,
- (2) a compound of 1 or 2 or more, selected from the group comprising following (a)-(h),
  - (a) other glucokinase activator,
  - (b) bis-guanide,
  - (c) PPAR agonist,
  - (d) insulin,
  - (e) somatostatin,
  - (f)  $\alpha$ -glucosidase inhibitor,
  - (g) insulin, and
  - (h) DPF-IV (dipeptidyl peptidase IV) inhibitor
- (3) a pharmacologically acceptable carrier.

21. A glucokinase activator containing as effective ingredient a compound in accordance with any one of Claims 1-19 or pharmacologically acceptable salts thereof.

22. A therapeutic and/or preventive agent of diabetes mellitus containing as effective ingredient a compound in accordance with any one of Claims 1-20 or pharmacologically acceptable salts thereof.

23. A therapeutic and/or preventive agent of obesity containing as effective ingredient a compound in accordance with any one of Claims 1-20 or pharmacologically acceptable salts thereof.



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